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THE SHATTUCK LECTURE

THE CLINICAL SIGNIFICANCE OF SOME PECULIARITIES OF THE CIRCULATION IN THE KIDNEYS, LIVER, LUNGS AND HEART*

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REFLECTION on the functional significance of the valves in the veins and in the heart led Colombo and Cesalpino to postulate a circulatory system in place of the long-accepted tidal flow of blood from the liver and heart. These anatomic peculiarities of the vascular system were also emphasized by Harvey, who first gave a quantitative description of the motion of the blood, based on the structure of the human heart and on experiments on living animals. In the past three decades more progress has been made in the quantitative study of the circulation of the viscera of man and animals than had been achieved in the previous three centuries. Much of this advance has been made possible by new technical methods, but data of some interest have also been obtained by the injection or perfusion of human organs post mortem by means of a technic that was possible even in the days of Harvey, and decisive answers have been given by animal experiments of a relatively crude and simple nature. Both methods were used to obtain quantitative answers to the query, What is the need of this organ for blood and what is the capacity of its vascular bed?

The blood supply of an organ must meet its needs during maximal activity. In muscles, the heart and digestive glands such as the parotid gland and the pancreas the need for oxygen during activity is many times that under basal conditions. A complete description of the circulation of an organ, in health or disease, must include an estimate of the oxygen needs, basal and maximal, the capacity of the vascular bed and the volume flow under varying conditions. The rates of flow during life are of utmost interest, and in the kidneys, liver and brain they can now be measured with some accuracy in unanesthetized men as well as in animals. The measurement of capacity for post-mortem flow will be most informative if it can be compared with rates of flow measured during life, just as all post-mortem studies in the past have been given significance by correlation with careful clinical observation.

THE KIDNEYS

The kidneys may well be described as the organs that "work while you sleep." Their blood flow and excretory work are maximal under basal conditions and during fever, but drop off during effort, falling to extremely low levels when the body is violently active or under such stresses as are imposed by shock or hemorrhage.[1, 2] One might say that the function and blood flow depend on how much blood can be spared from other tissues. This paradox of behavior was the first and most remarkable discovery made with the modern technics for measuring blood flow in the organs of an intact, unanesthetized animal or those of man.

Most observers agree that renal blood flow and oxygen uptake are not related to excretory activity, but their conclusions are based on experiments that did not evoke a wide range of variations in osmotic work. The rat can secrete urine with a 10 per cent urea content, and the osmotic work is then almost sixty times as great as that of the kidneys of a rat excreting dilute urine with only 0.1 per cent urea.[3] The oxygen consumption of the kidneys is augmented only 22 per cent with this enormous increase in osmotic work, but the caloric equivalent of the extra oxygen used is five times as great as that of the extra osmotic work performed (Table 1). In other words, the efficiency with which this extra osmotic work can be handled by the kidneys is 20 per cent — a high level for any vital process. The efficiency of their work when excreting dilute

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urine is quite low — only 0.08 per cent, as compared with 3.8 per cent for their work at the heaviest load. The rise in efficiency as work increases explains why, in the usual experiments on dogs and men, no relation between work and oxygen use can be detected.

It is not possible to measure the heat value for all the secretory work of the kidneys. Only the minimal possible amount is given by a study of urea concentration, but this is probably a considerable fraction of the total work. In any event, the extra oxygen consumed by the kidneys after changing from a low-protein to a high-protein fever-producing substances even in infinitesimal traces.

There have been several reports on perfusion of human kidneys with physiologic saline solution or with serum, but when the rate of Diodrast clearance was measured it became obvious that the flow calculated by aqueous perfusion was only 10 to 20 per cent of the blood flow during life. By making sure that the renal vessels had passed out of rigor, and perfusing with oil, to avoid edema formation, Cox and Dock[9] obtained in kidneys of young men rates of perfusion comparable with the most rapid rates observed when Diodrast was excreted during

TABLE 1. *Relation of Renal Osmotic Work* to the Oxygen Needs of the Rat and Its Kidney.*

SUBJECT	OXYGEN UPTAKE		HEAT EQUIVALENTS	
	BY ANIMAL	BY KIDNEY	FOR RENAL OXYGEN	FOR OSMOTIC WORK ON UREA
	cc./min.	*cc./min.*	*cal./min.*	*cal./min.*
Control animal	4.0	0.21	1.05	00.0009
Animal fed 74 per cent casein diet	5.6	(0.22)	(1.10)	(00.0036)
Animal excreting 10 per cent urea	4.1	0.26	1.30	00.0500

*Work forced by feeding of urea and restriction of water intake.

intake is too small to be detected.[4] This change of diet leads to hypertrophy of the kidneys, and after certain types of renal injury a high-protein diet may seriously jeopardize their recovery.[6] Such a diet supplies not only urea but also aromatic acids, which the kidneys actively secrete five times as effectively as they filter off and concentrate urea.[1] It may well be that these aromatic acids stimulate hypertrophy and the increase in blood flow noted in kidneys at the onset of hypertrophy.[6]

The oxygen used by the rat's kidneys secreting 10 per cent urea is only 0.2 cc. per gram per minute. The human kidneys probably never take up more than 0.1 cc. per gram per minute,[7] which could be supplied by a flow of 2 cc. of normal blood, leaving the renal venous blood still 70 per cent saturated with oxygen. The rates of excretion of Diodrast and aromatic acids by human kidneys prove that the basal flow must be at least 4 cc. per gram per minute. During the reaction to a pyrogen, such as typhoid vaccine, given intravenously the flow is almost 10 cc. per gram per minute, even though fever is prevented by premedication with amidopyrin.[1] On the other hand, no significant rise in renal blood flow occurs with arterial anoxia due to high altitude or to low oxygen content of the alveolar air.[8] The renal blood flow, which is many times greater than that necessary to supply the oxygen used by the kidneys, varies with the need to excrete substances noxious to the body. It is noteworthy that phenolic compounds are eliminated five times as efficiently as urea, and that maximal renal flow is evoked by fever. This gave us a method for determining with some accuracy the effect of disease on the capacity of the vascular bed in various organs.

This method was applied, in 1939, to the study of the vascular bed of the kidneys in hypertension. At that time most of the outstanding investigators of renal physiology and pathology had enthusiastically or tentatively accepted the thesis that nearly all hypertensive patients had significant renal arteriosclerosis, and the corollary that nearly all hypertension was due to renal vascular disease.

In chronic uremia, whether due to pyelitis, nephritis or severe vascular disease, the perfusion rates were found to be low — less than 10 per cent of normal. Even in the absence of hypertension or uremia there was a decrease in the vascular bed with advancing age. But in the kidneys of hypertensive patients dying of stroke, coronary disease, heart failure or some intercurrent illness we usually found perfusion rates equal to those of normotensive subjects, and often as high as those of normotensive persons of the same age.[9] We concluded, as have those who later determined flow during reaction to pyrogen in hypertensive patients, that in most cases the hypertension precedes any organic renal lesion.

The renal blood flow measured during life shows great fluctuations in normal subjects and even greater ones in many hypertensive persons. The true capacity of the renal bed can perhaps be measured only post mortem. The clinical fact of greatest importance is that hypertension is not

usually compensatory to renal arteriosclerosis and therefore a "good thing." It is a disturbance of vasomotor tone, probably varying greatly in its origin in different patients, or even in the same patient at different times. What complex interplay exists between the kidneys and the vasomotor center can be dimly perceived and remains to be elucidated.

Studies on the kidneys in shock have cast a new light on the old experiments on renal hypertension. A decrease in blood flow to the kidneys, whether due to a clamp on the renal artery or to shock, leads to a remarkable series of events.[8, 10] The most startling and unique is a decrease in renal metabolism and oxygen use roughly proportional to the decrease in flow of blood in the kidneys. The kidneys not only work while we sleep but also sleep when we are struggling to maintain life. When the renal blood flow is 10 per cent of normal, renal oxygen use is only 10 per cent of normal, and the blood in the renal vein is no more depleted of oxygen than under basal conditions.[8] When renal blood flow is arrested and later released, the vascular bed of the kidneys is not widely dilated, as it is in a limb or in other viscera after temporary complete ischemia. In the latter sites, the flow instantly rises to many times the basal rate when the artery is released; in the dog it takes nearly an hour for renal vasoconstriction to pass off and for blood flow and metabolism to return to normal after ten minutes of complete arterial block.[11]

Renal vasoconstriction in dogs and in men occurs after hemorrhage or shock. In man, it takes place in heart failure, or even when an erect posture, with a resulting decrease in cardiac output, is assumed[12]; it also occurs whenever pain, fear or anxiety is suffered.[1] At the times when other tissues require a large part of the cardiac output, the kidneys reduce both their extravagant demand for blood and their use of oxygen. Thus, they accumulate no oxygen debt.

Tigerstedt showed that the kidneys contained a heat-labile protein that acted as a vasoconstrictor. More recently, it has been demonstrated that renin is a protein-splitting enzyme, capable both of liberating a pressor amine from one of the globulins of the plasma and of inhibiting the oxygen uptake of isolated slices of renal cortex.[13] In rabbits, even after repeated injections have exhausted its vasoconstrictor action, renin causes an intense diuresis of fluid with about the composition of plasma filtrate.[14] In a word, it stops tubular reabsorption as effectively as cyanide. Shock apparently leads to the release, in the kidneys, of an inhibitor of renal metabolism that also causes renal vasoconstriction and may cause vasoconstriction generally.

It is worth emphasizing that anoxia has no such effect on the kidneys. When arterial oxygen saturation is low, the uptake of oxygen by the kidneys is normal and renal venous blood is profoundly unsaturated; renal blood flow increases slightly.[8] No hypertension follows arterial anoxia. The mechanism for reducing renal metabolism and causing vasoconstriction in the kidneys is set in play only by lowering of the renal arterial pressure or pulse pressure, or by raising of the interstitial pressure in the kidneys. Obviously, such a mechanism can be set off only by acting on a sensitive structure in the vascular bed of the kidneys.

An anatomic structure that might serve such a purpose had been noted in many mammalian kidneys by the histologists, just as the valves of the heart and veins were seen by many anatomists long before Colombo, Cesalpino and Harvey were aware of their functional significance. In this case it was Goormaghtigh,[15] of Belgium, who suggested, in 1939, that the renal pressor mechanism was probably related to the peculiar cells in the afferent arteriole of each glomerulus and the plaque of closely crowded epithelial cells in the distal convolution at the point where it touched the glomerular hilus. This structure takes different forms in various species. It shows unusual cytoplasmic granules, mitotic figures and even hypertrophy in animals subjected to acute renal ischemia.[1, 16] Changes in the juxtaglomerular tissue have also been noted after renal trauma and even after shock due to adrenalectomy.[17] In 1943 hyperplasia of this tissue was noted in kidneys of men who had been in shock for several days before death,[18] and photomicrographs were made of such changes in the material at the Army Medical Museum (Figs. 1 and 2). Goormaghtigh[19] reported this change in similar material seen in Europe. No such changes are seen in chronic renal hypertension of dogs or rabbits, or in human hypertension of long standing.

Renin may be detected in the blood in some cases of shock and of acute hypertension, but it is not found even in the renal venous blood in chronic hypertension.[20] This makes it probable that this renal mechanism was evolved in relation to shock and hemorrhage, which are common hazards of all mammals under natural conditions, but was revealed in the laboratory by throttling of the renal artery — a phenomenon that has no natural analogy in the pathology of rabbits and dogs. The pressor mechanism is perhaps less important than the inhibition of renal metabolism. This protects the kidneys even from many hours of ischemia, whereas muscles and other structures are seriously affected by shorter periods of arterial block, and the brain is destroyed by even a few minutes of ischemia. Dogs' kidneys completely recover from two hours of total ischemia, and in 50 per cent of animals even after four hours of arterial block.[21]

The relations of juxtaglomerular tissue and renin are not known; possibly, the arterioles release a substance that activates renin precursor in the cortical epithelium. Renin escaping from the epithelial part of the juxtaglomerular apparatus, the

macula densa, may act on the glomerulus and cause efferent arteriolar constriction. The relation of this entire mechanism to chronic renal hypertension is obscure, for in the chronic disorder no circulating vasoconstrictor substance can be demonstrated. Increased vasoconstriction in chronic renal hypertension is certainly mediated through the central

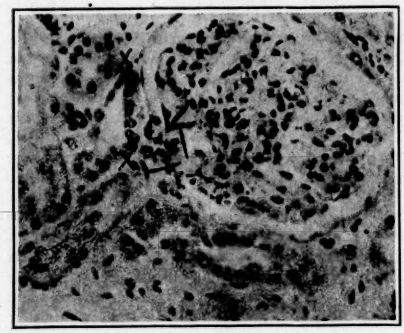

FIGURE 1. *The Glomerulus and Juxtaglomerular Tissue of a Normal Man Who Met a Sudden Death from Accident.*

The macula densa (X-X) *is a closely packed group of epithelial cells on the side of the distal convoluted tubule that touches the hilus of the glomerulus. The arteriolar cells, above and to the left of the lines, are shown by the arrow.*

nervous system, but by humoral and not by reflex stimulation of the vasomotor center.[22–24] When one recalls that minute quantities of pyrogen alter the "set" of the heat-regulating center, it is easy to believe that minute quantities of a substance from abnormal kidneys may alter the "set" of the vasomotor center.

THE LIVER

A kidney is the most marvelous anatomic structure in the body, its complexities being more awe inspiring than the thigh joints, which Solomon described as the "work of the hands of a cunning workman." The liver, on the contrary, is one of the simplest glandular structures in the body. Its oxygen uptake is determined by its metabolic activity, and in the rat rises from less than 0.1 cc. per gram per minute on a protein-free diet to more than twice that amount on a diet with a 74 per cent protein content.[4] The specific dynamic action of protein, or the rise in total metabolism after a protein meal, is due almost entirely to this intense hepatic activity (Table 2). The clinician, accustomed to prescribing rest for ailing men or organs, would predict that high-protein diets, by adding to metabolic activity, would retard recovery of diseased livers, and since no effect of such diets on renal metabolism has been demonstrated, the logical clinician would not reduce the protein intake in kidney disease. Experience has, of course, shown that in both hepatitis and cirrhosis a high-protein diet is beneficial, even though it makes the liver "work" harder. On the other hand, there is striking evidence that such a diet further injures kidneys in some species of animals with experimental nephritis, even though it does not appreciably increase the oxygen requirement of the kidneys.[5]

The blood flow of the liver in man is about 1 cc. per gram per minute.[25] This supply comes from two sources, the portal vein, with a pressure equivalent to 10 to 20 mm. of mercury, and the hepatic artery, with a pressure of 100 mm. or higher. In man all the portal flow may be diverted into the inferior vena cava without damage to the liver, and

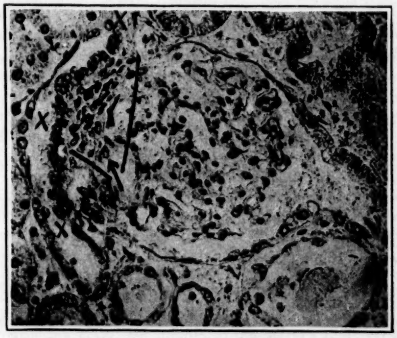

FIGURE 2. *Findings in the Kidney of a Man Who Lived for Five Days, in Severe Shock, after Injury.*

The long, unusually cellular macula densa (X-X-X), *and the large mass of cells in the arteriolar wall* (*arrow*), *are characteristic.*

in dogs ligation of the hepatic artery causes no apparent damage. Such ligation may have serious effects on the liver in a patient with chronic biliary-tract disease. Arterial lesions are rare in the liver, as contrasted with the heart or kidney of man, and chief interest in the vascular bed of the liver is aroused by the severe vascular derangement seen in cirrhosis.

Few have questioned the relation between portal hypertension, with splenomegaly, esophageal varices and ascites, and a reduction in the portal bed by scar tissue. But no proof of such a reduction in portal bed had been offered, when, in 1941, the livers were perfused with oil post mortem.[26] This

technic revealed in normal livers a capacity for flow well above the rates measured subsequently by Bradley and his colleagues[25] in men under basal conditions, using a catheter in the hepatic vein and a constant infusion of bromsulfalein.

Although anatomic studies indicate that the hepatic arterioles and the portal venules enter the sinuses of the liver lobule separately, the rate of perfusion through the normal portal vein drops a third when pressure in the hepatic artery is raised from 0 to 100 mm. during a double perfusion with oil, with portal inflow at 20 mm. In the livers of patients with alcoholic cirrhosis the portal flow fell, on the average, 78 per cent when flow at 100 mm. was established in the hepatic artery. This phenomenon was least marked in the cirrhoses not associated with chronic alcoholism, in which portal flow per gram fell, on the average, only 21 per cent. In many cirrhotic livers, decreases in portal perfusibility were noted when arterial pressure was 0. The lowest portal flow in a normal liver from an aged subject was 850 cc. per minute corrected to viscosity of blood, whereas in the cirrhotic liver with the poorest flow the rate was 480 cc. In two cirrhotic patients with enlarged livers the portal perfusibility was equal to the highest rate — 1700 cc. per minute—in the liver of a normal young man. Loss of liver substance requiring a blood supply, scarring in portal areas and narrowing of sinuses by swelling of parenchyma may contribute to the decrease in portal perfusibility. The lowest perfusion rate, 180 cc. per minute, was observed in a patient with acute alcoholism whose liver weighed 3820 gm., in whom no cirrhosis had developed. It was our impression that portal perfusion was usually normal in cases with much perilobular scarring but with little fatty change or necrosis of the parenchyma (Table 3).

The capacity for hepatic arterial inflow, when portal flow was established, reached 1100 cc. per minute in young normal subjects, 500 in old normal subjects and in patients with nonalcoholic cirrhosis, and rose to 1600 cc. per minute in those with alcoholic cirrhosis, averaging 1360 cc. in the last group. This is interpreted as confirming Herrick's[27] report of deranged portal-hepatic arterial ratios in cirrhosis. This is presumably due to the development of numerous minute arteriovenous fistulas analogous to the spider angiomas in the skin. The increased arterial flow is also borne out by the x-ray films of hepatic arterial beds injected post mortem with radio-opaque jelly (Figs. 3 and 4). The hyperplastic bed, which is most striking in alcoholic patients, is unusual in the others. Further information comes from Dr. Roy Cohn,[28] who observed the portal pressure during laparotomy in 4 cases of advanced cirrhosis. On occlusion of the hepatic artery for a brief period, the portal pressure fell 21 to 29 per cent, or the equivalent of 7 to 11 cm. of water. During the operation, the systemic systolic arterial pressure was not over 80 in these desperately sick patients so that the effect of the hepatic arterial inflow was less than it would have been with normal levels of pressure. Even after occlusion of the

TABLE 2. *Oxygen Needs of Tissues in the Intact Rat.*

SUBJECT	OXYGEN UPTAKE				
	BY ANIMAL	BY HIND QUARTERS	BY LIVER AND GASTRO-INTESTINAL TRACT	BY KIDNEY	BY HEART
	cc./min.	*cc./min.*	*cc./min.*	*cc./min.*	*cc./min.*
Control animal	4.0	0.35	0.9	0.2	0.4
Animal fed 74 per cent casein diet	5.6	0.38	2.3	0.2	(0.4)
Hyperthyroid animal	6.0	0.50	1.4	(0.3)	0.6

TABLE 3. *Estimated Capacity for Blood Flow in Human Livers (Based on Perfusion with Oil Post Mortem).*

CONDITION OF LIVER	WEIGHT OF LIVER	BLOOD FLOW			
		HEPATIC ARTERY*	PORTAL VEIN†	PORTAL VEIN‡	TOTAL
	kg.	*cc./min.*	*cc./min.*	*cc./min.*	*cc./min.*
Normal	1.6	800	1450	1000	1800
Fatty	3.8	700	180	~80	620
Cirrhotic (alcoholic)	2.1	1360	1000	270	1630
Cirrhotic (nonalcoholic)	2.2	550	1100	900	1490

*Pressure of 100.
†Pressure of 20, with artery closed.
‡Pressure of 20, with artery open.

hepatic artery, however, the portal pressure did not fall to normal in any of these cases, so that arteriovenous fistulas were not the main cause of portal hypertension.

I have seen only 2 cases of Banti's disease accompanied by portal hypertension without portal or splenic thromboses and with histologically normal livers. The only conceivable explanation is a congenital defect in the communications of the portal and hepatic arteries, with telangiectasia in the lobules. This could be determined during life by the fall of portal pressure to normal on occlusion of the hepatic artery, and post mortem by double perfusion or even by hepatic arterial injection. So far, no such studies have been reported.

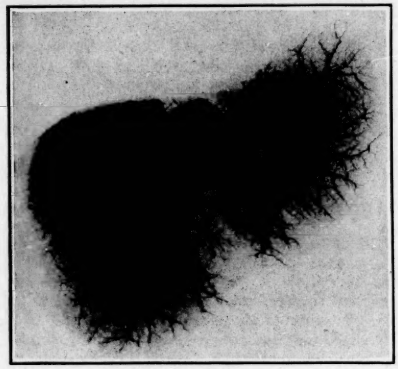

FIGURE 3. *Hepatic Arterial Bed, after Lead-Gelatin Injection, in the Normal Liver, as Visualized by X-rays.*

To what extent hepatic arterial flow is increased in chronic portal hypertension in various types of cirrhosis can best be determined by observations made during operations to provide portocaval anastomosis. When such arteriovenous fistulas are important factors, a complete portocaval shunt is obviously preferable to one between the splenic and the renal vein, for the latter does not close off the leak between the artery and the portal vein. It is to be hoped that surgeons will soon provide data on the fall of portal pressure with arterial occlusion in various types of liver disease, and especially in the Banti syndrome. In this connection one recalls the following comment of Sir Thomas Lewis[29]:

> Surgeons, if they would, could contribute heavily to clinical science. The special opportunities for observation presenting themselves during the progress of operations may be noted; they are not utilized as they might be. Such investigations . . . must remain purely incidental, and must always be conducted within strictly prudent bounds.

Another anomaly of the hepatic circulation that occurs in dogs — but not in cats, rodents, herbivora or man — is worth notice, since it has led to some interesting confusion in pharmacologic study. The dog has a muscular sphincter at the outlet of the hepatic vein, and spasm of this sphincter, evoked by histamine[30] and to a lesser degree by digitalis,[31] leads to a pooling of blood in the liver and portal bed, a fall in the systemic venous pressure and a marked reduction in cardiac output. Digitalis causes a fall of venous pressure and cardiac output in normal men, but the decrease is much less striking than that in dogs. In describing the hepatic element in the dog's response to digitalis, Tainter and Dock[31] took pains to point out that no such action could be postulated as contributing to the effect of digitalis in cardiac failure in man.

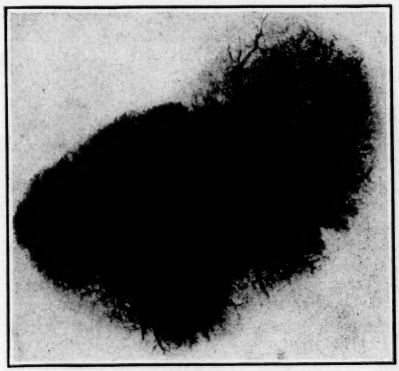

FIGURE 4. *Hepatic Arterial Bed from a Chronic Alcoholic Patient with Portal Cirrhosis.*
Note the extensive hyperplasia.

THE LUNGS

The blood flow through the lungs was the first to be measured. In 1870 Fick pointed out that by division of the oxygen uptake or carbon dioxide output by the difference in gas content of blood from the right and left sides of the heart the flow through the lungs could be determined. This was actually done, in dogs, sixteen years later by Grehant and Quinquaud and in horses during exercise, rest and digestion by Zuntz.

Up to 1923 this technic had not been used in North America, nor had it been employed to study the effects of disease. In that year two house officers at the Peter Bent Brigham Hospital used this method to measure the blood flow through the collapsed lung and the opposite lung in experi-

mental pneumothorax.[32] They found that less than a fifth of the cardiac output went through the collapsed lung, and thus ended a controversy, based on indirect and conflicting evidence, that had lasted thirty years. They also utilized the procedure to demonstrate the increased cardiac output occurring with experimental arteriovenous fistulas.[33] A flood of papers on the use of this method immediately followed; by 1930 Baumann had used the technic of ventricular puncture in man, and in 1941 Cournand and his co-workers began the catheterization of the right side of the heart that has opened a new chapter in the measurement of blood flow through the lungs in health and disease. By simultaneous measurement of right ventricular pressure the resistance offered by the pulmonary vascular bed can be measured. So far, no one has collected data, based on perfusion with oil post mortem, on the effect of varying degrees of collapse, distention and pulmonic pressure on the capacity of the vascular bed of the lungs of subjects of different ages and with various pulmonary lesions.

Although it is difficult to obtain quantitative data on collateral between the pulmonic and bronchial circulations by double perfusion, it has been possible to learn much by injection with radio-opaque or deeply colored jellies. Wood and his associates[34] in the Department of Pathology at Stanford University demonstrated extensive hyperplasia of the bronchial arterial bed and anastomosis with the pulmonary system in ulcerative tuberculosis, bronchiectasis and lung abscess, and in bronchogenic but not in metastatic cancer. At Cornell, anastomoses were demonstrated between the pulmonic and bronchial veins in normal adults, as well as extensive hyperplasia and varices in the submucous plexus of bronchial veins in cases of mitral stenosis.[35] This established the source for the brisk hemoptysis that occurs in these patients with no evidence of infarction or intense pulmonary congestion.

Because the lungs occupy a large space and the blood circulates through them at a relatively low pressure, posture greatly alters the flow and the quantity of blood in the apex and base or in the dorsal and ventral parts. Posture also alters the volume flow of blood through the lung. On reclining, the blood that fills the veins below the diaphragm is no longer held back by gravity, and the effective venous pressure, the quantity of blood in the lungs and the output of the heart are increased, the last by as much as 30 per cent in some subjects.

The venous blood in the lungs must return to the left ventricle, which has its center of mass near the ventral chest surface and the diaphragm, slightly to the left of the midline. Because of the effect of gravity on this flow, venous pressure at the bases, expressed in its equivalent of water, is 20 to 30 cm. greater than that at the apex of subjects in the orthopneic position. When the patient is in the right semirecumbent posture, frequent with cardiac patients, the venous pressure in the lateral and basal parts of the right lung is 10 to 20 cm. higher than that in any part of the left lung. These simple facts are of paramount importance in explaining the frequency of basal pulmonary edema and of right-sided hydrothorax in cases of cardiac failure, since the formation of tissue fluid increases rapidly with the rise in venous pressure.[36]

The flow of lymph also increases with the rise in venous pressure, and the dilution of toxic substances and the removal of bacteria or dusts, such as silica, is most rapid and effective at the base of the lungs. At the apex, not only is the venous pressure low but also the arterial inflow is compromised when adults are sitting or standing. The systolic pressure in the right ventricle is 18 to 30 in recumbent subjects.[37] It is perhaps only 12 to 25 when the patient is sitting, and the column of blood from the ventricle to the upper part of the lungs then exerts a pressure equally great. There is always a fall in pressure along the course of the arteries, and this must be more marked on the right side because the right pulmonary artery arises at an acute angle from the direction of flow in the pulmonic conus and pursues a tortuous path around the aorta. Consequently, the apical fourth of the left lung and the apical third of the right can have practically no blood flow for two thirds of each day in the life of sedentary people. Silica, coal dust, bacteria and toxins cannot be removed effectively when lymph flow ceases. Antibodies formed by the body or antibiotics given parenterally will not reach this zone. Oxygen tension will be high because aeration continues and the unsaturated blood from the systemic veins is not pumped up by the right ventricle. All this creates ideal conditions for tubercle bacilli, and it is not remarkable that in this region tuberculosis flourishes even when, in spite of positive findings in the sputum and constant seeding to all parts of the lung, no progressive lesion appears at the bases for many years.[38, 39]

Although it is impossible to determine the relative significance of high venous pressures at the base and low arterial inflow at the apex in altering the resistance to tuberculosis, it is noteworthy that in rabbits and in cattle progressive lesions of tuberculosis are most numerous at a site anatomically opposite from the apex — namely, the dorsal and juxtadiaphragmatic part of the lower lobe.[40, 41] Here, too, arterial inflow is reduced and venous pressure greatly lowered, since this portion of the lungs is highest above the heart in four-footed beasts. The high incidence of tuberculosis in cases of congenital pulmonary stenosis, which greatly lowers pulmonic arterial pressure, and the low incidence of active tuberculosis in mitral stenosis, with pulmonic pressure two to six times normal,[37] strongly support the thesis that arterial inflow is of crucial importance. The effect of gravity on the lungs thus explains the remarkable efficacy of rest

flat in bed in the treatment of apical tuberculosis, as contrasted with miliary or other types of the disease. It should be noted that antibiotics will be least effective in reaching apical lesions when patients are allowed to sit up most of the day, so that the type of management introduced by Joseph Pratt will continue to be of value even after effective chemotherapy for tuberculosis has been developed.

The peculiar relations of the pulmonary circulation to the gravitational pull are of great practical effect in the management of both congestive failure and pulmonary tuberculosis — the two most frequent natural causes of death between childhood and senescence. In heart failure the orthopneic posture makes life tolerable; in apical tuberculosis it may make recovery impossible.

The Heart

The oxygen requirements of the isolated hearts of rats, dogs and other mammals have been measured, as have the coronary flows in several species and in the human heart revived after death. In the rat, the oxygen used by the heart even in the hyperthyroid state with pulse rates over 300 is not over 0.6 cc. per gram per minute.[42] The oxygen used by the human heart probably never exceeds 0.1 cc. per gram per minute and is believed to be about 0.06 cc. during vigorous activity. That quantity can be supplied by a blood flow of 1 cc. per minute, which leaves the venous blood still half saturated with oxygen. This maintains an oxygen tension adequate to allow diffusion of oxygen into the center of a muscle fiber twice the diameter of those in a greatly hypertrophied heart.

Cardiac hypertrophy is a mechanism of great adaptability. In arterial hypertension of gradual evolution the wall of the left ventricle becomes thicker, but the diastolic capacity does not increase; the fibers are thicker but no longer than normal.[43] But when increased output must be maintained, as in hyperthyroidism, anemia or valvular disease, the fibers grow longer, and the chamber becomes more capacious. Loss of efficiency, the usual cause of heart failure, leads to an increase in both length and thickness of the fibers. Hypertrophy occurs rapidly, and when the stimulus is removed the muscle returns quickly to its normal weight.[44] One of the problems of great importance to the cardiologist is whether the coronary bed adapts itself to the growth of the myocardium with the same nicety as the muscle fibers adapt themselves to the load imposed on them. Several authors have suggested that congestive failure occurred because hypertrophy outstripped the growth of the coronary bed. Kountz,[45] perfusing revived human hearts, observed control rates of flow up to 3 cc. per gram per minute under vasodilator drugs. He found the rates low in hearts revived after death from cardiac failure, but in such hearts only low perfusion pressures could be maintained.

The perfusion of hearts with oil has yielded decisive data, and in this case the data so far have not been supplemented even by the wielders of the vascular catheters. There has, of course, never been any doubt that occlusion or severe narrowing of the large coronary arteries that lie in the epicardium must reduce the flow to the heart muscle. The only perfusion rates below 0.7 cc. per gram per minute, calculated as blood flow at the equivalent of 100 mm. of mercury, were observed in hearts with severe coronary atherosclerosis; the lowest rate, 0.2 cc. per minute, was in a heart with two large arteries occluded and constricted regions in most epicardial branches. In hypertrophy without coronary disease the flow rates were more than adequate to provide oxygen in excess of the needs of the thickest fibers.[46]

As hearts grow from infancy to maturity the coronary perfusibility per gram of tissue decreases. After maturity, the average perfusibility of hearts of normal weight decreases. The flow at ages sixty-six to eighty-five was 30 per cent less than that at ages twenty-five to forty. In hypertrophied hearts the flow per gram also decreases, but this appears merely as a smooth extension of the curve of the decline in the normally growing heart up to maturity. Even in the largest hearts of old men, when the main branches were patent the flow at 100 mm. never fell below 0.7 cc. per gram per minute. At the patient's usual diastolic pressure, the calculated flow fell below that level in only 2 cases of aortic insufficiency. Neither in the heart with the lowest calculated flow — 0.45 cc. at the patient's diastolic pressure — nor in any of the others had there been angina during life or fatty change in the myocardium post mortem.[46] These are the classic symptomatic and anatomic sequelae of cardiac anoxia, whether due to coronary disease or severe anemia.

Anatomic studies had given an equivocal answer to the question of coronary flow in cardiac hypertrophy. Injection of the arteries by Schlesinger's technic demonstrates a striking hyperplasia of the visible arteries, whereas capillary counts show no reduction in loops per fiber, and a decrease in capillary loops per gram of muscle.[47] It should be recalled that resistance to flow decreases as the fourth power of the radius of the vessel increases. Thus a 10 per cent increase in diameter of the minute vessels would cause an increase of nearly 50 per cent in flow; a 19 per cent increase would double it. Changes in caliber unperceived by the anatomist may greatly alter the perfusibility of an organ such as the heart, and the only real test of perfusibility is perfusion.

Perfusion shows that the possible flow in the heart of a healthy young man may be as much as 500 cc. per minute, whereas in the hearts of older patients with hypertension the ventricles, two or three times

heavier, have possible rates of flow of 700 to 1000 cc. The coronary bed adapts itself to the needs of the organ it serves, as would be expected from the development of the vasculature in other sites — around the coarcted aorta, in the pregnant uterus and even in tumors. Having seen the intercostal arteries, many centimeters away from the tissue that needed blood, so dilated as a result of coarctation that the ribs themselves became eroded,[48] one would be surprised if the arteries in the myocardium could not hypertrophy to provide blood needed by hypertrophied muscle or by a region supplied by an occluded coronary branch.

The coronary bed is peculiarly liable to atherosclerosis, at least in populations with dietaries such as ours. Nearly a fifth of the sedentary men of North America die because of the vulnerability of the epicardial branches of the coronary system. Even in manual workers and elderly women the death rate from coronary disease is high. Occlusion may occur when the aorta and the rest of the arteries are in faultless condition, particularly in men under the age of fifty.[49]

Even at birth these arteries have intimal layers thicker than those of any other vessels of similar size in the body, and this natural intimal thickness increases throughout life even if atherosclerosis fails to occur. In a small series, male infants were found to have far more striking intimal cushions than females.[50] Perhaps the earlier onset of disease and far higher mortality in males is due to this anatomic peculiarity. Men also drink more milk and eat more eggs than women, but the frequency of gallstones in women in North America makes it unlikely that the sex difference is due to lower blood cholesterol levels. In the Orient coronary disease and cholesterol stones are rare; there, men have more gallstones (of the calcium bilirubinate type) than women do.[51] It may be concluded that atherosclerosis will occur in people with meat and dairy products in the regular diet; its predilection for the coronary arteries, in men and in certain families, may be due to an anatomic anomaly present at birth.

Using the oil perfusion technic and also glass microspheres of various sizes, Prinzmetal and his co-workers[52, 53] have studied the volume of collateral flow and the caliber of the cross channels in the heart. This has given further evidence of the adaptability of the coronary circulation under the stresses imposed by disease. Because of this adaptability normal cardiac function may be maintained for years after the occlusion of the largest arteries in the heart.

* * *

This description of the circulatory peculiarities of some of the viscera has emphasized the phases of investigation with which I am most familiar. The introduction of the vascular catheter and the use of radioactive isotopes have opened up a vast program of study of the circulation in various organs of normal and of diseased men, and the description of this problem will be greatly modified in the next decade. Yet it is instructive to see that much can still be learned by the use of simple methods of post-mortem study and animal experiment.

Perfusion with oil serves to measure the capacity for flow through many organs. Perhaps the most urgent problem connected with the study of aging is the disseminated cortical atrophy that is associated with loss of memory, originality and judgment. Methods for measuring the cerebral flow during life are now being perfected, but by perfusion it is possible to measure flow through each major subdivision of the cerebral vascular bed and to correlate changes with the histology of the brain and with clinical observations on cerebration and total cerebral flow. It is to be hoped that this method will be applied in all clinics where blood flow is being measured during life. In most such centers post-mortem material from patients who have been subjected to elaborate quantitative studies is being examined exactly as it might have been in the days of Virchow or Rokitanski.

During the last year of a life largely devoted to bettering the care of the sick and the education of physicians, George Cheyne Shattuck made a generous gift for the purpose of improving the teaching of morbid anatomy at Harvard. This eminent practitioner, from his own experience and from the work of such contemporaries as Bright and Addison, fully realized the supreme value of complete post-mortem examination correlated with well planned clinical study. New methods for clinical study merely make more essential the evolution of a morbid anatomy adequate to maintain this effective correlation. Even with the use of methods available to all for the past seventy years, it is possible for pathologists and even practitioners to make essential contributions to an understanding of the diseases that remain the "captains of the men of death."

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DWARFISM IN HEALTHY CHILDREN: ITS POSSIBLE RELATION TO EMOTIONAL, NUTRITIONAL AND ENDOCRINE DISTURBANCES*

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CHILDREN in good health who are receiving an adequate diet tend to follow a relatively standard pattern of growth and maturation. Although moderate deviations from the average trend are commonly considered to be normal physiologic variations, extreme deviations suggest that some abnormality exists. In the past few years more than 100 abnormally short children have been encountered in the pediatric clinics of this hospital. In approximately 50 per cent of these patients the stunted growth could be related to a definite disturbance in the pulmonary, cardiovascular, gastrointestinal, renal, hepatic, skeletal or endocrinologic system. There remained, however, a group of 28 boys and 23 girls, two and a half to fifteen years of age, in whom no such abnormality could be found. The present paper is the result of attempts to discover and eradicate the cause of stunted growth in such patients.

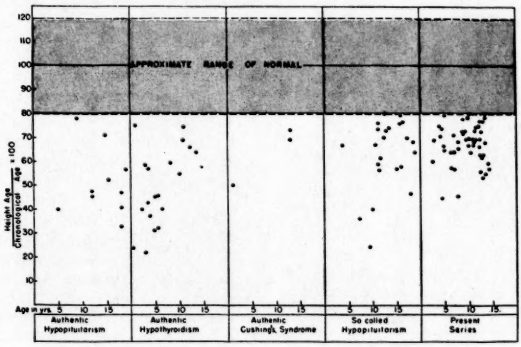

FIGURE 1. *Heights of Various Types of Dwarfed Children.*

Results are expressed as height age divided by chronologic age times 100 (ordinate) and are plotted against approximate chronologic age (abscissa). A height-age ratio of 100 indicates that the subject is of average normal height for the age and sex. The shaded area gives the approximate range of normal.

Description of Patients

Figure 1 presents the data on the stature of these patients and gives comparative information on the height of patients dwarfed as the result of authentic hypopituitarism,[1–11] hypothyroidism[12] and Cushing's syndrome[12–15] respectively. A number of the so-called "pituitary dwarfs" of the literature are also represented.[3, 16–25] The results are expressed in terms of height age times 100 divided by actual age, the height age of each subject being the average age of normal children of the same height and sex.[26] None of the patients under discussion had a height age that was more than 80 per cent of the actual age. Expressed in another manner, all the present subjects were 5 cm. or more shorter than 90 per cent of

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normal children of the same sex and age. It can also be seen that the patients were approximately as short as those with authentic endocrine dwarfism and that they were no taller than most of the so-called "pituitary dwarfs" of the literature.

Information on the stature of the parents and siblings of these patients may be of interest. Data on the height of the parents were available in 39 of 51 cases. In 74 per cent the father was reported to be more than 158 cm. and the mother more than 152 cm. tall. Nineteen patients had younger siblings, 84 per cent of whom were as tall as or taller than the patients. In only 5 per cent of cases were there close relatives whose stature was reported to be remarkably short. This information appeared to provide little justification for the assumption that the small stature of the children was necessarily due to hereditary limitation of growth capacity.

Figure 2 gives information concerning the weight of these patients. To relate their weight to their height, the results are presented as weight age times 100 divided by height age. A ratio of 85 to 115 is considered to be approximately within normal limits (Fig. 2, Group B). Higher ratios suggest that the subject is overweight (Fig. 2, Group A), whereas lower ratios suggest that he is underweight (Fig. 2, Group C) for his height. The values presented indicate that about 70 per cent of the patients in the series belonged to Group B; the remaining 30 per cent were underweight (Group C). In contrast, the patients with authentic endocrine dwarfism tended to be of at least average normal weight for height (a weight-age ratio of more than 100), and about half — those in Group A — were overweight (a ratio of more than 115) according to this definition.

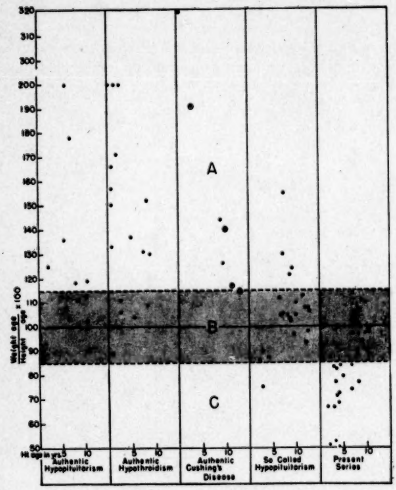

FIGURE 2. *Weight Relative to Height of Various Types of Dwarfed Children.*

Results are expressed as weight divided by height age times 100 (ordinate) and plotted against height age (abscissa). The upper clear area (A) includes patients considered to be overweight for their height; the shaded area (B) suggests that the weight is within normal limits for height; the lower clear area (C) includes patients who are underweight for height. The circled points represent children with Cushing's syndrome who were not dwarfed[37-39] and so emphasize the fact that there is a tendency to be overweight in this condition.

The weight of a child relative to his height is not always an adequate index of the subcutaneous fat stores.[31, 32] Thus, although there was a tendency for the patients who were relatively more underweight to be thin, clinical examination indicated that all but 3 of the children whose weight was within normal limits for height also tended to have scanty subcutaneous tissue stores (Fig. 3).

Figure 4 presents information concerning the skeletal maturation of the various types of patients. The skeletal age was estimated from roentgenograms of the hand and wrist according to Todd's standards. The results are expressed in the following ratio: skeletal age times 100 divided by actual age. It is evident that the skeletal age of the majority of the patients was retarded behind the actual age to approximately the same degree as the height age. In this respect the patients did not differ consistently from the authentic endocrine or the so-called "pituitary dwarfs." There was, however, a tendency for the hypothyroid children to show the greatest and those in the present series and the so-called "hypopituitary patients" the least degrees of retardation in skeletal maturation.

Nutritional History

Since it did not seem appropriate to explain the small stature of these patients a priori by a hereditary limitation in growth capacity and because no physical diseases could be discovered, the average daily food intake of 29 patients was evaluated by means of detailed dietary histories obtained through procedures described elsewhere.[33] The results are considered below from two points of view: the average daily caloric intake and the average intake of certain building materials — namely, protein and calcium. Generally speaking the nutritional histories of the majority of these children indicated clearly that they were difficult feeding problems and had been so for the major portion of their lives, in many cases since infancy.

Caloric intake. Figures 5 and 6 present values for the estimated average caloric intake of each of the girls and boys on whom nutritional histories were obtained. In these figures the continuous curves

running upward from left to right represent the average caloric intake of normal children of corresponding ages, whereas the interrupted curves stand for a standard deviation below the average and approximate the lower limit of normal for this community.[34, 35] It can be seen that the caloric intake of 85 per cent of the patients was at or below the lower limit of normal for chronologic age. These

Protein intake. Figure 7 sets forth estimations of the average daily protein intake in the cases in which nutritional histories were obtained. The continuous curve running upward from left to right represents the protein allowances for boys recommended by the Food and Nutrition Board of the National Research Council; the same curve gives the recommended allowances for girls up to eleven years,

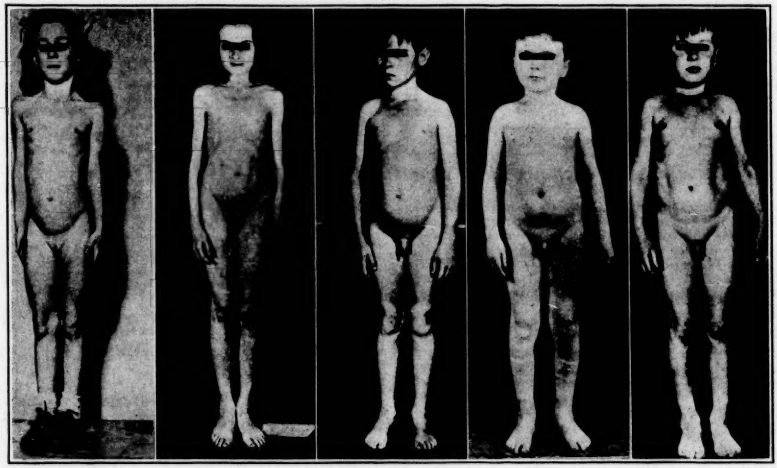

FIGURE 3. *Physical Appearance of Various Types of Dwarfed Children.*

Patient A, *aged six and a half years, was underweight for her height (Group C, Fig. 2) and was very thin. Patient* B, *aged thirteen and a half years, was an extremely thin member of Group B (weight within theoretical normal limits for height). Patient* C, *aged twelve and a half years, was of normal weight for his height (Group B) and appeared to be adequately nourished. Patient* D, *was eleven years old was overweight for his height (Group A) and was moderately obese. Patient* E, *aged twelve years and an example of authentic hypopituitarism, was a member of Group A and was moderately obese.*

data, however, do not take into consideration the influence of subnormal size on caloric requirements. Presumably, the requirements should be scaled down somewhat to correct for the fact that these patients had a smaller protoplasmic mass and surface area than normal children of the same age. On the other hand, the caloric requirements may easily have been greater than those of normal children of the same size or height to enable them to catch up to normal and to meet the larger caloric requirements for activity reported for older children.[36] When such variables as these are considered, it seems reasonable that the trends shown in Figures 5 and 6 are valid. Certainly, they are in keeping with the clinical observation that the majority of the children had poor subcutaneous fat stores.

whereas the interrupted line at the right indicates allowances for older girls. The values were lower on the average than the allowance for age recommended by the National Research Council. When calculated in relation to body weight, however, the average daily intake of protein of these patients was 2.2 gm. per kilogram of body weight, with a range of 1.5 to 3.6 gm. There was essentially no difference between the average daily values found for children of normal weight (Group B, 2.1 gm. per kilogram of body weight) and those for underweight subjects (Group C, 2.4 gm.).

There is evidence that children can grow — that is, they can be in positive nitrogen balance — when the daily intake of protein is as little as 0.7 gm. per kilogram of body weight.[37] In this connection it is

of interest that the daily increase in body protein during the major part of childhood amounts to only

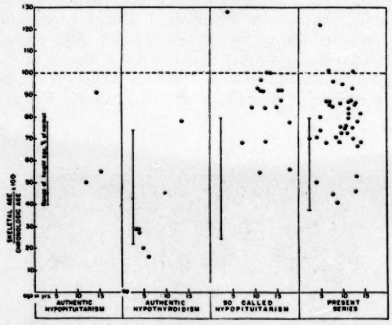

FIGURE 4. *Skeletal Development of Various Types of Dwarfed Children.*

The results are expressed as skeletal age divided by chronologic age times 100 (ordinate) plotted against chronologic age (abscissa). The vertical lines in each section indicate the range of height ages divided by chronologic ages times 100 shown in Figure 1. The interrupted horizontal line indicates where the bone age (and height age) plots would fall if they corresponded to the average normal for sex and age.

about 0.1 gm. per kilogram of body weight.[12] Viewed in this light, a daily protein intake of approximately 2 gm. per kilogram of body weight is apparently in excess of minimum growth requirements.

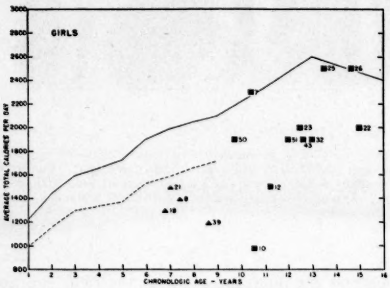

FIGURE 5. *Average Total Daily Caloric Intake for Girls (ordinate) Plotted against Chronologic Age (abscissa).*

The squares stand for children of normal weight for their height (Group B, Fig. 2), and the triangles represent children who were underweight for their height (Group C, Fig. 2). The numbers adjacent to these symbols are case numbers. The continuous curve running upward from left to right gives the approximate average normal total caloric intake for children of corresponding age and sex. The lower interrupted curve is one standard deviation below the average normal and gives the approximate lower limit of normal. These normal data for children one to nine years of age are based on data of Beal, Burke and Stuart[34]; the data for children older than nine years are National Research Council daily allowances modified to fit the fact that girls have their maximum growth spurt and hence caloric requirements at thirteen years, whereas boys have thirs at about fifteen years.

Evaluation of the adequacy of the protein intake, however, also demands simultaneous consideration of the caloric intake. The primary nutritional requirement of the body is for calories to meet the energy requirement. When the caloric balance becomes negative, there is an increased tendency for dietary protein to be used for fuel rather than for growth. Thus, a protein intake that is ample for growth under conditions of caloric adequacy may be

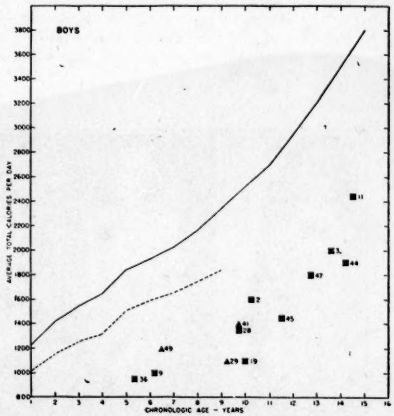

FIGURE 6. *Average Total Daily Caloric Intake for Boys Plotted against Chronologic Age.*

The legend of Figure 5 explains the chart.

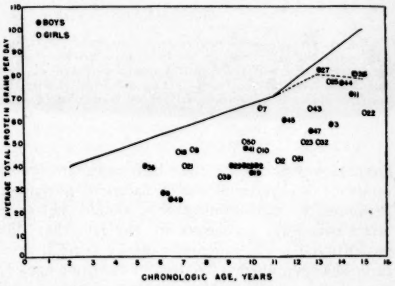

FIGURE 7. *Average Total Daily Protein Intake for Boys and Girls Plotted against Chronologic Age.*

The continuous curve running upward from left to right gives approximately the allowance recommended by the National Research Council for boys. The same curve gives values for girls up to eleven years, and the interrupted line at the right-hand end of the continuous curve gives values for older girls.

insufficient under conditions of caloric inadequacy. Consequently, it seems probable that in our patients, the protein intake per se was not incompatible with growth, but that it may have been rendered inadequate by the poor caloric intake.

Calcium intake. Calcium as a limiting dietary factor was also considered. In 18 of the 29 subjects the intake of this mineral was more than the daily minimum requirement of 600 to 800 mg. for children of preschool age.[38] The remaining 11 patients were found to be taking 200 to 600 mg. daily. It should be mentioned that the recommended allowance for calcium increases with age through the peak of the adolescent growth spurt and that these children ranged in chronologic age between two and fifteen years. It may also be stated that the minimum allowances referred to above were recommended for subjects whose stores were already saturated. It has been calculated that the daily calcium growth of normal children amounts to between about 5 and 7.5 mg. per kilogram of body weight.[39] Expressed in terms of total retention per day, this amounts to approximately 68 mg. in normal four-year-old subjects and increases to a maximum of 190 mg. in normal sixteen-year-old children. The average daily intake of the 11 children receiving a total of 600 mg. or less per day was 22 mg. per kilogram of body weight — the range being 10 to 35 mg. It is of interest that growing children habituated to a low-calcium diet can store in their bodies as much as 89 per cent of a small calcium intake — 200 to 250 mg. per day.[40] These facts suggest that a small child receiving 200 mg. of calcium per day can absorb and retain 175 mg., which exceeds normal growth requirements for such a child. Although it is difficult to draw more than tentative conclusions from such observations, the foregoing information indicates that few, if any, of the patients had a calcium intake that was incompatible with normal growth. This was supported by the fact that neither x-ray films of the wrist nor determinations of serum calcium, phosphorus and alkaline phosphatase values showed changes suggestive of rickets.

Again, relating the calcium intake to the protein intake, or more properly to the nitrogen balance, is pertinent. Bone growth occurs as the result of protein matrix formation. Secondarily, calcium salts are deposited in the matrix. Consequently, when skeletal protein anabolism is limited, the amount of calcium that can be deposited is necessarily limited.

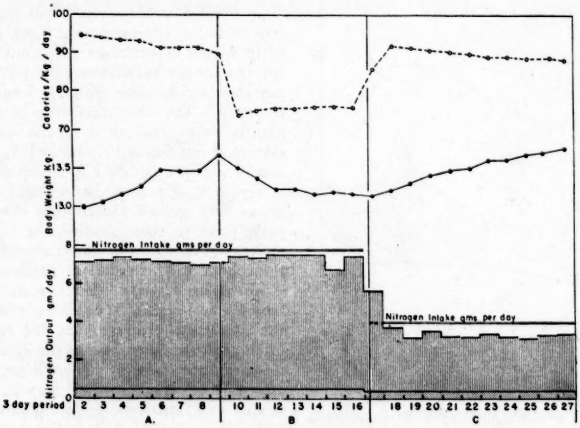

FIGURE 8. *Changes in Body Weight and Nitrogen Balance Induced by Variations in Caloric Intake in a Thin, Underweight Dwarfed Child (Patient* A, Fig. 3).

In the upper portion of the chart, the caloric intake per kilogram per day is indicated by hollow circles connected by an interrupted line. The black circles connected by a solid line represent body-weight measurements. In the lower portion of the chart are set forth nitrogen-balance data. The distance from the baseline to the double horizontal line gives the nitrogen intake. The cross-hatched area adjacent to the baseline gives the nitrogen output in the stool, and the vertically lined area above this gives the output in the urine. The balance is indicated by the distance between the intake and the urine plus stool output.

Effect of Calories on Nitrogen Balance

The foregoing nutritional studies thus suggested that caloric deficiency was the cause of the retarded growth in certain patients. To investigate further the possible significance of this idea, one of the underweight and apparently calorically undernourished children of Group C was admitted to the Metabolic Ward of the Massachusetts General Hospital for a study of the relation of variations in caloric and in protein intake to the growth rate as measured by the nitrogen balance. The technics used were similar to those reported elsewhere.[41] The appearance of this child at the time of admission is presented in Figure 3*A*. Figure 8 sets forth the chief metabolic observations. During Period A the patient received a diet calculated to yield approximately 1200 calories and 48 gm. of protein a day. On this regime she gained weight at the rate of about 35 gm. and retained nitrogen at the rate of about 0.6 gm. daily. During Period B the patient received the same protein intake, but the daily content of the diet was reduced to 1000 calories. On this diet the patient lost body weight and showed a less positive nitrogen balance (about 0.4 gm. per day). Finally, in Period C the intake was restored to a level of 1200 calories, but the daily protein intake was reduced to 25 gm., or 1.9 gm. per kilogram of body weight. On this diet she gained weight at a rate of 30 gm. and stored nitrogen at the increased and rapid rate of 0.7 gm. a day. Not shown in the figure are numerous measurements of the basal metabolic rate and of the rate of insensible weight loss. Neither of these measurements gave grossly abnormal values, and neither showed any striking changes during the course of these periods.

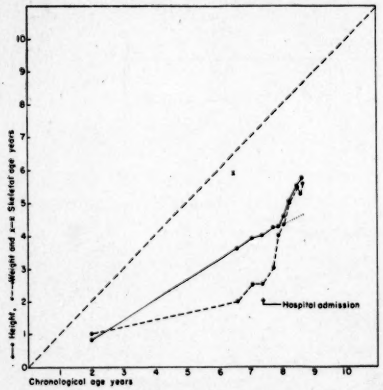

FIGURE 9. *Growth in Height and Gain in Weight of Same Patient before and after Hospital Admission When Dietary Intake Was Increased.*

Results are expressed as height age (black circles connected by solid line) and weight age (white circles connected by interrupted line) plotted according to the scale on the ordinate against chronologic age (abscissa). One measurement of skeletal age is represented (X). *The diagonal dashed line indicates where the height, weight and skeletal age symbols should fall if the patient was average normal for her age and sex.*

These observations suggest that in this child the caloric intake was a more important determinant of the rate of growth (protein anabolism as reflected by the nitrogen balance) than the protein intake. They further confirm the thesis that a daily protein intake of approximately 2 gm. per kilogram of body weight is sufficient to permit rapid nitrogen storage, for the anabolism of 0.7 gm. of nitrogen per day should yield approximately 7 kg. of true muscle in a year.[42] The other implication of these findings — namely, that this child should grow rapidly in stature if continuously provided with an adequate diet — is borne out by the measurements recorded in Figure 9. It is seen that whereas the patient had grown and gained exceedingly slowly during the years prior to these studies, she gained and grew extremely fast during the succeeding months, in the course of which she ate much more food.

Viewed as a whole, therefore, these clinical, nutritional and metabolic studies coupled with data in the literature[18] suggest that the retarded growth of the thin patients of the present series was due primarily to caloric malnutrition. Because the calories were inadequate, it may be that the body tended to adapt itself by using protein for energy rather than growth. This is discussed below.

Psychiatric and Social Studies

The possibility that some of these children were calorically undernourished led to attempts by the nutritionists and medical staff to improve the diet of thin patients in Groups B and C. These efforts met with little success, often because the children could not be interested in the idea of eating more food. In 4 of 21 cases this lack of interest could be attributed to moderately marked mental deficiency (Fig. 10). On the other hand, no explanation was provided by the information obtained in the other 17. Accordingly, these patients were studied from the social-service and psychiatric points of view. For control purposes 7 dwarfed but apparently well nourished patients were likewise studied (Fig. 10).

As indicated in the figure, the patients fell into six groups. In Group I nothing remarkable was found. As mentioned above, the children of Group II were found to be moderately mentally deficient as evidenced by an intelligence quotient of about 70. Group III was made up of patients from families whose economic resources were markedly limited and in which the mother's intellectual equipment

was not sufficient to enable her to carry through adequate housekeeping and nutritional management of the child. In Group IV it was found that for emotional reasons the mother was unable to accept and perform her nurturing functions with the child. Some of these mothers had not wanted the pregnancy and had emotionally rejected the child after birth. In others adjustment to womanhood in general and motherhood in particular was poor. In still others poor marital adjustment and hostility to the husband led to hostile attitudes toward the child. In Group V, because of a "nervous breakdown" or delinquency on the part of the mother, the home situation was as seriously disturbed as in the preceding group. One mother was in jail because of indecent conduct. Another had had a psychotic reaction in the puerperium. The others had reactive depressions making them profoundly preoccupied with their own concerns and inaccessible to the children. The children of Group VI all had severe emotional reactions, with chronic grief* and anorexia due to a broken home brought about by death, divorce or desertion.

It will be noted that the incidence of social or psychiatric difficulties was remarkably high in the thin dwarfs. The control group of apparently well nourished dwarfs was too small to permit any clear analysis. The incidence of difficulties, however, was lower in the control subjects. Unfortunately, similar studies on run-of-the-mill hospital patients are not yet at hand. The need for such studies is clearly evident. Nevertheless, the available information suggests strongly that the thin dwarfs were undernourished either because of anorexia due to emotional disturbances or mental deficiency or because of a combination of such disturbances and poverty and ignorance on the part of the parents.

Although the period of follow-up study has been too short to warrant any detailed evaluation of psychiatric therapy, it can be said that such therapy has already been followed by a major improvement in appetite in 3 children of Groups B and C. After the change in appetite these children have shown a decided increase in the rate of weight gain and subsequently in the rates of growth and maturation. The patient presented in Figures 8 and 9 is an example. The prognosis for such successful psychotherapy is probably fair to good in about half the children studied to date.

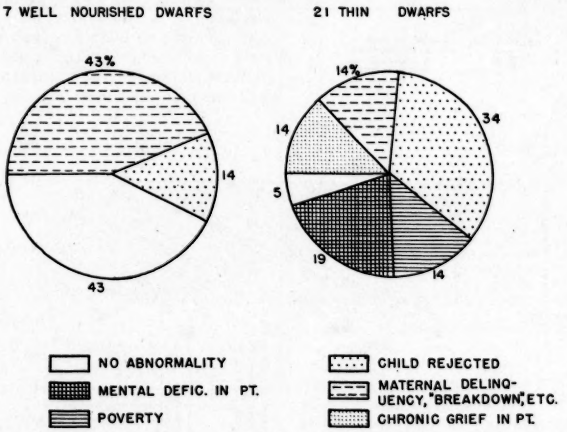

FIGURE 10. *Incidence of Mental Deficiency, Poverty and Various Emotional Disturbances in 21 Thin Dwarfs Compared with that in 7 Well Nourished Dwarfs.*

The Role of Growth Hormone

There is evidence that during the major part of childhood, growth in stature (protoplasmic anabolism) is dependent not only on the assimilation and transportation of building materials (protein, minerals and so forth) to the growing end organs but also on the presence of the pituitary growth hormone.[12] Growth defined as an increase in stature due to the construction of new skeletal (proto-

*This type of reaction has been described elsewhere by one of us (E. L.[40]).

plasmic) tissue proceeds exceedingly slowly in the absence of this hormone, even when the dietary intake is more than sufficient to meet the requirements for maintenance and growth. Under these circumstances the protein ingested is catabolized, and any surplus calories are stored as body fat. Contrariwise, provided there is an intake of building materials in excess of minimum maintenance requirements, growth can proceed under the influence of growth hormone even if the total caloric intake is insufficient to meet the total energy requirements.[12] Under such circumstances any caloric deficit is made up by the combustion of body fat.

According to these ideas it may be postulated that children such as the present patients in this series, who were ingesting every day 2 gm. of protein per kilogram of body weight, should have grown at a satisfactory rate had they been producing appropriate amounts of pituitary growth hormone. In other words, the slow growth of these children may have been due, in the final analysis, to a relative deficiency of pituitary growth hormone. Although it was impossible to test this theory by the administration of a potent preparation of pituitary growth hormone, it was possible to give the substitute protein anabolic agent — methyl testosterone* — to 4 thin patients of the present series, as well as to 4 similarly dwarfed but well nourished children. Following a control period of several months these patients were given 20 to 30 mg. of the drug by mouth daily for a period of about three months. The data in Figure 11 show that all were growing at an abnormally slow rate during the control period. During the period of therapy, on the other hand, there was universally a striking increase in growth rate to normal or superior levels. These observations indicate that the thin as well as the well nourished dwarfs were capable of normal growth rates. To the best of our knowledge this change in rate was not accompanied by important changes in appetite. The observations may also be interpreted as suggesting again that the ultimate cause of the abnormally slow growth during the control period was a relative deficiency of the naturally produced pituitary growth hormone.

Such a thesis is well supported by the evidence in the literature. It is known that malnutrition secondary to famine or to anorexia nervosa is accompanied by a tendency to amenorrhea, asper-

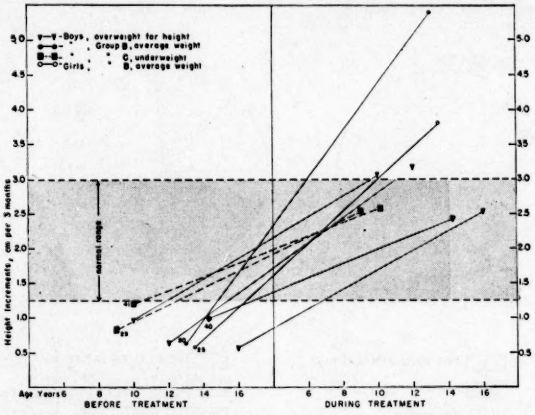

FIGURE 11. *Effect of Oral Methyl Testosterone Therapy on Growth Rates of 8 Dwarfed Children.*

Four of these children were well nourished, and 4 of them were thin. The rates of growth before treatment were observed over a period of at least six months. The rates of growth during treatment indicate the rates found during the first approximately three months after therapy was begun. The position of the symbols for each child relative to the abscissa indicates roughly the age of the patient at the time when therapy was started. The numbers beside the symbols are case numbers. The shaded area depicts the approximate normal limits of growth increments expressed, like the results, as centimeters per three months.

*Kindly supplied by Schering Corporation, Bloomfield, New Jersey.

matogenesis, retarded sexual maturation and the like.[44–47] These changes in all probability signify that the organism tends to adapt itself to nutritional privation by becoming relatively hypopituitary.

Recovery from Malnutrition Accompanied by Failure to Resume Normal Growth

These thoughts have a practical bearing on the problem presented by the few dwarfed but relatively heavier and apparently well nourished patients of the present series. The medical and nutritional histories obtained on some of these children suggested strongly that they had undergone a period of nutritional privation in earlier childhood. It is conceivable that such children adapted themselves to the malnutrition by a diminution in pituitary activity but failed to resume normal pituitary function when the diet improved. Patient C in

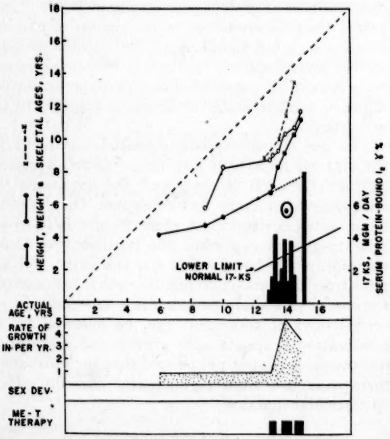
HEIGHT, WEIGHT & SKELETAL AGES, YRS.
LOWER LIMIT NORMAL 17-KS
17 KS., MGM. / DAY
SERUM PROTEIN-BOUND I, γ %
ACTUAL AGE, YRS
RATE OF GROWTH IN PER YR.
SEX DEV.
ME-T THERAPY

FIGURE 12. *Observations on the Growth in Height, Gain in Weight and Skeletal Maturation and 17-Ketosteroid Output of a Dwarfed Boy (Patient C, Fig. 3).*

This boy was eventually treated intermittently for a period of two years with 20 to 30 mg. of methyl testosterone daily by mouth. The form of this chart is similar to that of Figure 10.

Figure 3, as well as Figures 12 and 13, illustrates this possibility.

This patient was said to have been normal up to the age of four years. At that time his mother died, with the result that for approximately four years he had to shift for himself in the daytime while his father was away at work. During this period he is reported to have subsisted largely on coffee and doughnuts. When eight years of age he was found by a relative to be small and poorly nourished. Unfortunately, no early records of his weight are available. The first records of height (Fig. 12), however, show that he had grown very little between the ages of six and nine years. At about the eighth year he was adopted into another home, where he promptly gained much weight. Figure 12 shows that although he continued to gain in weight from the ninth to the thirteenth year, he failed to accomplish a corresponding increase in

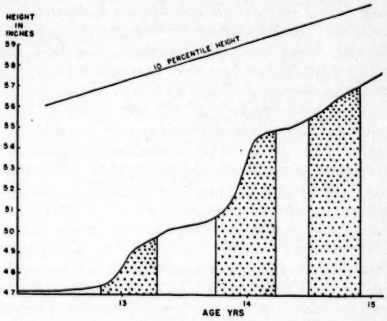

FIGURE 13. *Detailed Record of Increments in Height of Same Patient before, during (speckled areas) and After Periods of Methyl Testosterone Treatment.*

stature. Physical examination at the age of thirteen years revealed an apparently healthy, intelligent and well nourished, but abnormally small boy. There were no evidences of sex maturation. Ordinary clinical laboratory tests, as well as roentgenograms of the skull, disclosed nothing of note. The bone age was retarded four years. The urinary 17-ketosteroid output was likewise below normal limits.

In view of the fact that the nutrition seemed to be adequate, no attempt was made to stimulate growth by dietary therapy. Since the dwarfism, together with the retarded skeletal maturation and lowered urinary ketosteroid values, suggested a lack of normal pituitary activity, the patient was treated intermittently with the substitute growth hormone, methyl testosterone, over a period of two years. This was given by mouth in daily doses of between 20 and 30 mg. Figure 12 reveals that this therapy promptly induced a marked acceleration in growth rate. There was a corresponding increase in the rates of weight gain and skeletal maturation. The urinary 17-ketosteroid output also tended to rise from abnormally low to normal levels during periods of methyl testosterone therapy. Figure 13 gives more detailed information and shows again that prior to this medication, the growth rate was exceedingly slow. During the first period on methyl testos-

terone, the rate of growth increased markedly, but returned to essentially pretreatment levels when the drug was discontinued. This deceleration of growth indicated that the first growth spurt was not spontaneous. A similar response occurred during the second course of therapy, but this time there was no decline in growth rate when the drug was stopped. The administration of the drug for the third and final time had no appreciable effect on the rate of growth. From this time on the patient continued to show satisfactory progress in growth, weight gain, skeletal and sexual maturation and urinary ketosteroid excretion. These observations suggest strongly that he had in fact been suffering from a functional type of hypopituitarism and that during the therapy he resumed normal pituitary function.

A similar progress in growth was noted in 4 other patients of Group B following one or two courses of methyl testosterone of three months' duration. It is tempting to postulate, therefore, that testosterone not only directly stimulates protoplasmic anabolism but also promotes increased pituitary activity. This contention is supported by the changes in urinary 17-ketosteroid output observed in the patient described above. Methyl testosterone is not per se metabolized and excreted as a urinary 17-ketosteroid.[48] Therefore, the increase in ketosteroid output noted during periods of methyl testosterone therapy presumably reflects an increase in the rate of production of 17-ketosteroid precursors by the glands that normally produce them — namely, the adrenal cortices or testes, or both. Since the activities of the glands are controlled by the anterior portion of the pituitary body, the rise in ketosteroid output appears to signify that an increase in pituitary activity had taken place. It is entirely possible that a similar increase in pituitary activity would have occurred spontaneously at a later date.

Mention should probably be made of the alternative possibility that malnutrition or emotional disturbances, or both, induced an overproduction of anti-growth hormones by the adrenal cortex — the "S" hormone of Albright.[30] This seems relatively unlikely. Consideration of other explanations for the retarded growth of the patients seems inappropriate at present. The purposes of this paper will have been fulfilled if the problems presented by physically normal, dwarfed children gain wider attention.

Summary

A sizable number of physically sound but abnormally small children were investigated. It was noted that some were grossly underweight for their height and that the great majority appeared to have scanty subcutaneous fat stores. Nutritional studies revealed that although the intake of building materials such as protein was probably adequate for growth, the total caloric intake appeared to be undesirably low. In the majority of cases this predominantly caloric malnutrition appeared to be related to anorexia secondary to emotional disturbances. In 3 cases correction of emotional difficulties resulted in an improvement in appetite that was followed, in turn, by a rapid gain in weight and an appreciable increase in the rates of growth and maturation.

A few children failed to resume normal growth when the dietary inadequacies had been corrected. Furthermore, it was found that the growth rate of both poorly nourished and well nourished dwarfs could be increased markedly by the administration of a protein anabolic or growth hormone — namely, methyl testosterone — without any evident change in diet. In a few well nourished dwarfs growth continued spontaneously at a satisfactory rate after one or two short courses of testosterone therapy. These observations coupled with the evidence of the literature concerning the value of anabolic hormones and especially of the pituitary growth hormone as determinants of growth rate during childhood[12] suggested that the dwarfism in this group of children was due to a functional hypopituitarism occasioned by the limited caloric intake. If this thesis is correct, it may be assumed that this hypopituitarism reflected a homeostatic or adaptive reaction to the malnutrition.

The use of testosterone as initial treatment for the stunted growth of nutritional dwarfs seems illogical; correction of emotional and nutritional inadequacies commands first attention. On the other hand, when correction of these factors fails to accelerate growth and when the possibility of hypothyroidism has been ruled out, the daily oral administration of about 20 mg. of methyl testosterone for one or two short periods may, especially in retarded boys of adolescent age, be followed by an acceleration in spontaneous growth and maturation processes. It cannot yet be said that such hormonal therapy is free from permanently harmful effects on testicular function.

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A CLINICAL SYNDROME SIMULATING POLIOMYELITIS

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DURING the week August 11 to 18, 1946, a total of 34 new cases of poliomyelitis were reported in Nebraska, 176 cases having been reported for that year. With serious epidemics in the neighboring States of Minnesota, South Dakota and Colorado, there was considerable apprehension on the part of the people of this area. On the front page each day the press reported the new cases and the precautions to be taken. In letters to editors, readers asked for a spraying of the City with DDT, and offered new epidemiologic theories. The terror that past generations manifested toward "the plague" was displayed toward poliomyelitis. Precautions dictated by fears were at times extreme, particularly in this year, when transmission by contact and carriers had been stressed. In this situation of social anxiety, it was not remarkable that evidence of neurotic behavior was found.

During the week when 34 new cases of poliomyelitis appeared in the State, 5 cases closely simulating poliomyelitis were observed in private practice, in 4 of which the patients had hysterical paralysis of one or more extremities. These cases are presented below because of a similarity in the situational and psychologic mechanisms involved.

It is believed that an elucidation of the clinical features of these cases may serve to accent the importance of anxiety and other emotional factors in suspected cases of poliomyelitis. These cases also illustrate the value of determining the nature of the paralysis, for purposes of diagnosis as well as for treatment.

CASE REPORTS

CASE 1. L. B., a 25-year-old housewife, was referred because of the development of a headache, chiefly occipital, stiffness of the neck and weakness in the left arm.

A nephew who had been living with the patient's family on a farm had developed poliomyelitis 5 days previously and had been sent to Lincoln, Nebraska, for hospital treatment. This experience had been disturbing to the patient and to the neighbors of the surrounding countryside, one of whom, in declining to pay her a visit, stated that she would be glad to come to the patient's home after the first frost.

Examination revealed the cranial nerves to be normal, except for some difficulty in moving the head from side to side, which was attributed to muscle stiffness. There was no particular stiffness in flexion of the head on the neck. The motor status showed the left arm to be held in a position of flexion and to be weak and limited in movements, but increased in muscle tone. The left leg also showed a minor degree of diffusely distributed weakness. The deep reflexes were equal and active. Superficial reflexes were present and normal in type. Sensory status revealed a left hemihypalgesia.

At the time of admission the patient had a temperature of 99.4°F. and after the examination the nature of her illness had been explained to her, she was considerably relieved. She was given 0.4 gm. of sodium amytal (6 gr.) that night, and on the next morning, with encouragement, she showed a full range of motor power and was allowed to return home.

CASE 2. G. H., a 33-year-old housewife, was seen as an outpatient at the Lutheran Hospital because of backache and weakness of the left leg. Her physician reported a temperature of 99.6°F.

The patient stated that in 1939 her daughter had developed poliomyelitis, which had seemed to appear suddenly, the first awareness of the disease being when she fell out of a chair during an illness that had been considered to be influenza. For the previous day the patient had complained of backache and weakness in the left leg. In spite of her ability to walk from the car to the hospital, she was confident that she had poliomyelitis.

Neurologic examination revealed the cranial nerves to be normal. Motor status showed a questionable diffuse type of weakness in the left leg. The deep reflexes were equal and active. Superficial reflexes were present, without any abnormal forms. Sensory status was normal.

The patient, who was reassured that she did not have poliomyelitis, was obviously relieved emotionally and left the hospital secure and symptom free.

CASE 3. E. B., a 23-year-old housewife, was seen at the hospital because of the loss of motor power in both legs, particularly the left.

Ten days prior to admission the patient had experienced an upper respiratory infection, from which she had appeared to recover. On the day before admission, she had gone to a celebration in a neighboring town and had returned that evening extremely tired. Shortly after going to bed, she became concerned because she was unable to move the left leg, and later noticed weakness in the right. The past history revealed that at the age of 12 she had had an episode of weakness in both legs, and during the course of her life there had been many manifestations of neurotic behavior.

On admission the temperature was 97.4°F. The patient did not seem to be under any particular tension and was quite composed. Neurologic examination showed the cranial nerves to be normal. Motor status revealed normal motor power in the upper extremities, but in both legs there was a weakness associated with increased muscle tone, more marked on the left side. There was limitation in movement, flexion and extension of the toes. The deep reflexes were bilaterally exaggerated. The superficial reflexes were normal in type, without pathologic manifestations. There was a bizarre type of sensory loss in the lower extremities that did not conform to any peripheral or segmental pattern.

The patient was assured that she did not have poliomyelitis, but when the nature of her illness was explained, she found the explanation impossible to accept on a functional basis. Behind the conversion features were personal and emotional problems of which this patient had little, if any, conscious appreciation. She was discharged on the day of admission.

CASE 4. R. S., a 24-year-old carpenter, was admitted to the hospital because of headache, stiffness in the neck and backache.

This patient had been exposed to a sister-in-law who had developed poliomyelitis about 3 weeks previously, and he came to the hospital greatly disturbed, the complaints mentioned above having developed on the preceding day.

Physical examination revealed a temperature of 98.8°F. The patient and his wife were obviously panicky and quite sure that the patient had poliomyelitis. Neurologic examination was entirely negative, except for some questionable stiffness in the neck. A lumbar puncture showed a normal spinal-fluid pressure, with 1 cell per cubic millimeter.

The patient was reassured that he did not have poliomyelitis, and the nature of the illness was explained to him. He was discharged on the day following admission.

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CASE 5. C. C., a 30-year-old housewife, was seen at the Douglas County Hospital because of inability to move the arms or legs.

The history disclosed that for several days the patient had been constipated and that on the morning of admission, while straining at stool, she passed a considerable amount of blood, which she described as making her feel weak and frightened. She lay down and was discovered to be feverish, and shortly thereafter called on a physician at his office. Because of the fever and muscle weakness, she was advised to report to the isolation ward. The past history was of significance, in that the patient had always been nervous and had just returned from a 3 weeks' stay at a hospital, where she had been treated for "nerves."

Physical examination revealed a temperature of 103°F., with redness of the throat. The patient appeared tense and apprehensive, expressing the hope that her children would not contract her illness. Neurologic examination showed the cranial nerves to be normal. There was a diffuse type of weakness of all four extremities that was slightly more marked in degree peripherally. The muscle tone was slightly increased. The deep reflexes of the arm were present and equal. The knee jerks were questionably present, and the left ankle jerk could not be definitely obtained. There was a bizarre type of hypalgesia in all four extremities that failed to follow any peripheral or segmental distribution. The sensory loss was more marked on the right side than on the left. Lumbar puncture showed a normal spinal-fluid pressure and 6 cells per cubic millimeter, without elevation in the protein.

It was explained to the patient that she had an upper respiratory infection, but not poliomyelitis, and the nature of the muscle weakness was described. With encouragement, she rapidly regained motor power and was discharged from the hospital after the pharyngitis had subsided.

DISCUSSION

A review of these cases reveals certain interesting correlations. Three patients had relatives who had developed poliomyelitis, 2 in the recent epidemic. Four had an elevation of temperature on admission, and all complained of pain either in the back or in the neck. In the 4 patients who showed weakness of one or more extremities, the weakness was associated with an increase rather than a decrease of muscle tone and with intact or exaggerated reflexes in all but 1. In 3 cases there were subjective or objective paresthesias. The recovery of motor power in all 4 cases was prompt following reassurance and an explanation of the nature of the illness.

A composite picture of the reported cases might be reconstructed as follows: a social attitude of marked anxiety precipitated by the development of poliomyelitis in the community; a marked intensification of anxiety by the appearance of poliomyelitis in the family group; the development of concern about exposure; subsequent development of an upper respiratory infection, with attendant symptoms, as well as the somatic expressions of anxiety in the form of neck stiffness, tightness in the throat, feelings of suffocation and weakness; and finally a localization of the weakness in one or more extremities as a conversion symptom, with a prompt return of function on reassurance and explanation.

In the treatment of this group of cases, certain preventive measures deserve consideration. First of all, a factual presentation of poliomyelitis by the press is indicated. If a daily report is to be made, it might best be presented in an accessible part of the paper other than the front page, unless some emergency exists. A special effort should be made to appease any unreasonable fears of members in a family in which a case of poliomyelitis has developed. When the syndrome described above develops with hysterical paralysis or other neurotic features simulating a poliomyelitis, reassurance effects a prompt symptomatic cure. The response to reassurance and explanation in the cases in which there was marked fear because of association or exposure to patients with the disease suggests that the motor loss had as its basis an overwhelming fear, which caused a dissociation in motor activity. It is as though the patient had become "paralyzed with fear." The more usual conversion mechanism found in hysterical paralyses seemed to be responsible in Case 3. The depth of psychotherapy needed depends on the dynamics of the individual case.

SUMMARY

Attention is called to the existing social attitudes toward poliomyelitis and to individual reactions to this anxiety-provoking situation.

Five cases of suspected poliomyelitis are reported that had many features in common, 4 patients presenting hysterical paralysis of one or more extremities. The course in these cases is described.

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ALLERGIC REACTION TO PENICILLIN

Report of a Case

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EXTRACTS prepared from various species of the dermatophytes show potent antigenic properties. Jadassohn,[1] using the Schultz–Dale technic, proved that pathogenic fungi contained not only species-specific antigens but also an antigenic fraction common to all species. Clinically, dermatologists have long been cognizant of explosive reactions from fungus toxins, manifested by generalized "ids" and by bullous eruptions. Therefore, it seemed probable that patients being treated with penicillin would exhibit allergic reactions, either to a common hyphomycetic allergin or to a specific penicillin allergin.

Reactions to penicillin are clinically infrequent, but do occur. A recent case focused attention on this subject and prompted a brief survey of the literature. Florey and Florey[2] encountered no reactions in 187 patients. In the 500 cases reported by the National Research Council,[3] urticaria was observed in 2.8 per cent, whereas in 209 cases reported by Lyons[4] the incidence was 5.7 per cent. Tests by Lyons for cutaneous and ophthalmic sensitivity during and after the reactive phase were negative, and precipitins were absent. Among the 182 patients of Stokes,[5] skin eruptions appeared in 0.8 per cent. Fifty-nine per cent of the 1418 syphilitic patients treated by Moore[6] exhibited Herxheimer reactions with fever and usually exacerbation of secondary skin lesions, and allergic eruptions appeared in 1 per cent. Dawson and Hobby[7] found skin reactions in 3 of 100 cases. Cormia[8] reported that of 2000 soldiers receiving prolonged penicillin treatment, 6 developed urticaria, 3 a serum-sickness syndrome, 2 erythematovesicular eruptions, 1 erythema nodosum, and 5 transient miliaria; skin tests were positive in 57 per cent of 116 persons tested. The development of symptoms of a low-grade fever, malaise, urticaria and transient edemas was noted by Haswell[9] in 4 of 56 patients receiving parenteral penicillin. Herrell[10] observed cutaneous sensitivity to skin tests in only 2 of 150 cases of clinical penicillin reactions.

The skin of many persons is known to be sensitive to various molds and mold products. Many cases of clinical contact dermatitis have been reported in the literature. Some of these may have been due to an underlying generalized, tuberculin type of sensitivity, such as that seen in the vesicular dermatophytids of the hands in patients with dermatophytosis of the feet. According to Epstein,[11] involvement of the epithelium does not necessarily make an eruption a true eczematous contact dermatitis, and not all dermatitis that is brought about by external contact is immunologically of the contact type. Pyle and Rattner[12] reported a case of dermatitis venenata of the face and genitalia in a pharmacy officer who reacted strongly with a patch test of crystalline penicillin. A similar case was presented by Binkley,[13] with a positive intradermal and patch test to the penicillin used. Satulsky,[14] Markson[15] and Bedford[16] reported cases of dermatitis of the eyelids with positive patch tests. Silvers[17] performed patch tests on a chemist with penicillin dermatitis of the eyelids and penis and found the test with commercial sodium penicillin positive, and that with crystalline sodium penicillin negative. Benkwith[18] and Schultz[19] observed allergic dermatitis of the eyelids from penicillin instillations, with positive intradermal and patch tests. Barker[20] reported the case of a medical officer who developed an acute dermatitis of the face while handling penicillin in a laboratory and who exhibited a positive patch test to the penicillin solution but not after the solution had been autoclaved. Michie[21] described an eczematous reaction to penicillin involving not only the ear being treated but also an almost healed leg wound to which penicillin powder had been applied. This patient exhibited a positive patch test. Vickers[22] demonstrated by a case report that penicillin powder can cause a dermatitis when sprinkled on local abrasions; his patient also had a positive patch test. Kleinfield,[23] Phillips[24] and Kern[25] reported allergic involvement of the palate and the pharynx in cases in which penicillin was administered orally; no patch tests were reported. Selinger[26] observed a dermatitis of the eyelids from penicillin eye drops, but the patch test was negative. Thirteen of 350 cases of various types of cutaneous lesions treated by Goldman[27] with penicillin ointment developed clinical contact dermatitis, 11 presenting positive patch tests.

In 1944 Criep[28] reported a case of massive urticaria after the injection of 200,000 units of penicillin in a patient who exhibited a positive intradermal test to the penicillin but a negative intradermal test to the spores. Barker[20] presented another case of massive urticarial reaction after the injection of penicillin, with a positive intradermal test to the penicillin solution. Tests with autoclaved solutions were negative. Morris[29] reported a case of bullous

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dermatitis following the injection of 100,000 units of penicillin; no tests were done. Strickland[30] observed a patient who developed during a second course of penicillin treatment an immediate severe generalized urticaria and angioneurotic edema. No skin tests were performed. Binkley[13] reported a case of dermatitis of the face with a negative intradermal test. When this patient was injected with 60,000 units intramuscularly, a papular dermatitis of the face, hands and feet followed and persisted for seven days. Flinn[31] described a patient who suffered a severe urticarial reaction from injections of one brand of penicillin, although clinically and by skin tests he was not allergic to one of the other brands. One of Goldman's[27] cases developed vesicular dermatitis from parenteral penicillin and exhibited an urticarial skin test reaction, a tuberculin type of reaction and a positive patch test. A case of clinical contact dermatitis observed by Truitt[32] demonstrated positive intradermal and patch tests followed in nine months by a tuberculin type of reaction. Graves[33] reported an acute vesicular reaction that began after the first injection of penicillin for a low-grade prostatitis and was followed by a superficial form of desquamation. This patient gave a positive intradermal test to 500 units of penicillin and to a 1:100 dilution of trichophyton. In a similar case the patient gave a negative intradermal reaction to penicillin and a positive reaction to the trichophyton extract. It was not decided whether the lesions were a manifestation of sensitivity to penicillin or some impurity in the penicillin solution used or were due to the too rapid liberation of toxic products from some unsuspected fungous or bacterial focus or to an alteration of local immunity that allowed dormant fungous spores to become active. In 3 of Goldman's[27] cases, with histories of recurrent mycotic dermatitis of the hands or feet, penicillin provoked a pompholyx-like dermatitis. It is interesting that of 17 patients with previous fungous disease observed by Cormia[8] 88 per cent showed an immediate reaction to intradermal tests with penicillin, although none had been treated previously with penicillin. Lamb[34] reported a case of syphilis under treatment with penicillin in which the patient developed a vesicular eruption of the fingers, penis and crural areas and gave a positive wheal-reaction intradermal test to penicillin. Another patient who during the course of penicillin injections for actinomycosis developed a vesicular eruption of the crural region, scrotum and webs of the fingers presented a negative intradermal test to penicillin and trichophyton but a positive intradermal test to oidiomycin. In 10 cases of skin eruptions treated by penicillin, Heinlein[35] found that the drug caused a marked aggravation of the existing skin eruptions, frequently associated with the appearance at other sites of new similar cutaneous manifestations accompanied by systemic reactions. This phenomenon was considered a manifestation of an underlying bacterial allergy. Price[36] reported a case of reaction to penicillin consisting of purpuric eruptions with subsequent wheals and arthralgia in which the patient gave a positive reaction to intracutaneous injections of serum with penicillin. Scratch and patch tests with penicillin solution were negative. Sullens[37] presented a case exhibiting urticaria, arthralgia and generalized lymphadenopathy that began six days after a second course of penicillin had been instituted; this patient presented a negative skin test to the penicillin solution, but the skin testing caused the appearance of urticarial lesions of the upper arm above the area of the test. Binkley's[13] case of dermatitis from penicillin presented no epidermal or intradermal sensitivity by cutaneous testing, but the patient had a papular edematous eruption of the hands and feet after a test intramuscular injection of penicillin.

Rostenberg[38,39] found that 5.5 per cent of 144 subjects gave a tuberculin type of sensitivity reaction to penicillin although they had had no previous contact with the drug. This spontaneous sensitivity seemed to have no eczematous or wheal component. He also reported that properly spaced intradermal injections of penicillin could cause a tuberculin type of sensitivity to develop; during sensitization such patients may develop urticarial reactions. It was not possible to demonstrate a passive transfer of the sensitivity exhibited by persons who showed a tuberculin type of reaction on first contact with penicillin. Epstein[11] reported a case of delayed tuberculin-type, infiltrated, itching reaction to both commercial and crystalline penicillin in a nurse who presented a clinical picture of contact sensitivity. All patch tests were negative except when the solution was applied to a site that had previously shown the eruption. Truitt[32] observed a case of clinical contact dermatitis with at first a positive immediate intradermal test but nine months later a positive tuberculin type of reaction. Claybon[40] presented a series of cases of presumed penicillin urticaria in which he was unable to obtain any positive penicillin tests. Likewise, 4 of 56 patients receiving injections of penicillin who developed allergic reactions resembling serum sickness were reported by Haswell[9] as giving negative patch, scratch and intradermal tests.

Case Report

A 52-year-old man, who had been hospitalized for 20 years with the diagnosis of dementia praecox, was admitted to the infirmary because of a cough and a fever of a few hours' duration.

Previous to the acute onset of these symptoms he had been free of any complaints, working about the hospital grounds every day. The family and personal histories were negative for asthma, hay fever, hives, eczema, angioneurotic edema or other symptoms suggestive of allergy. The record revealed that a dental check had just been completed, with negative x-ray studies for apical abscess or other dental infection. The patient had not been away from the hospital for months, and there was no contagious disease among his known contacts. There was no history of previous administration of penicillin.

Physical examination revealed a well developed man who was only moderately ill. The conjunctivas were slightly injected, the scleras were clear, and the pupils were round and regular and reacted to light and to distance. The ears were free of drainage, and the drums normal. The nasal passages were free of discharge, and the oropharynx showed no evidence of infection. There was no cervical adenopathy. Both lungs were resonant; there were a few rales, with an increase in bronchial quality to the breath sounds in the right axillary region. There was no demonstrable enlargement of the heart, the cardiac rhythm was regular, and there were no murmurs. Examination of the abdomen, skin and neuromuscular system was negative. The temperature was 104°F., and the respirations 24.

Examination of the chest showed a pneumonic lesion of homogenous density in the region of the right middle lobe that was diagnosed as lobar pneumonia. The remainder of the lung field was clear. Repeated throat smears and cultures revealed no pathologic organisms.

Examination of the blood disclosed a red-cell count of 3,830,000, with a hemoglobin of 85 per cent, and a white-cell count of 24,300, with 87 per cent neutrophils, 12 per cent lymphocytes and 1 per cent basophils. Repeated urinalyses were negative except for a rare pus cell. A serologic test for syphilis, repeated 3 weeks later, was negative.

The patient was placed on 30,000 units of penicillin every 3 hours. No other medicine was given. In 96 hours the temperature had descended to a normal level, and the chest was clearing clinically and on x-ray examination. On the 3rd day, a nonitching rash appeared, consisting of minute, closely packed red points, nonpapular in character, involving all portions of the body more or less simultaneously. The oropharynx and tongue exhibited no lesions. No adenopathy or vomiting was present. Rumpel–Leede's sign could not be elicited. After 24 hours the penicillin was discontinued, and the rash began to fade. Within 3 days, all erythema had disappeared, and extensive desquamation occurred, persisting for 5 days.

Contact patch tests with soap and with rubbing alcohol were negative. Passive transfer tests with commercial penicillin and crystalline penicillin produced, on the test subject, wheals with pseudopods that reached diameters of 2.5 cm. in 20 minutes and persisted for about 1 hour; serum and penicillin controls gave only areas of erythema about 0.6 cm. in diameter. It was not practical to do intradermal skin tests on the patient.

Pyle[41] has stated that in 4000 cases treated with penicillin he saw no rash similar to that observed in the case presented above. Goldman[42] noted a similar reaction in a physician. Moore[43] stated that among 25,000 patients in the nation-wide syphilis study there were perhaps 4 such cases.

A review of the literature suggests that penicillin should not be used for minor ailments. Patients who have previously been treated with penicillin and those who have had previous fungous infections should be closely watched. Skin testing should help to warn the physician of a potential allergic reaction, although not all physicians would agree with Cormia[8] that an immediate reaction 10 cm. in diameter contraindicates penicillin therapy. In general it is a wise policy to begin a course of penicillin injections with small dosages, to prevent possible aggravation of foci of infection. If the patient has areas of fungous infection, they should be treated locally at the same time as the penicillin is administered intramuscularly. When penicillin is used topically or administered orally the possibility of a contact type of sensitivity should always be kept in mind.

Summary

A review of the literature on allergic reactions to penicillin is presented, and a case of an apparent reaction is described. Caution in the administration of the drug for minor ailments is stressed, and the value of skin tests for sensitivity is discussed.

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MEDICAL PROGRESS

PHYSICAL MEDICINE

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DURING the war rapid developments occurred in the field of physical medicine. Activities included in this specialty have expanded to comprise more active and diversified treatment during convalescent stages of disease to ensure a speedy return of injured soldiers to combat or workmen to industry. In addition to widening, the field is also reaching greater depths through the establishment of research programs to investigate some of the fundamental problems of the effects of physical agents. Along with these advances it has become apparent that it is necessary for men to receive special training in physical medicine to understand properly the many different types of treatment to be prescribed and to direct adequately technicians, such as physical and occupational therapists and others working in rehabilitation. Special training is also necessary to aid in the proper integration of fundamental and clinical research in this field. Physical medicine can accordingly be said to have emerged as a distinct specialty, although the exact boundaries are still somewhat undefined. The need for specialists has far exceeded the supply. Only a few years ago less than fifty physicians in the country considered themselves as specialists, whereas at present approximately one hundred and fifty men are needed in the Veterans Administration and Army alone.

There has been considerable confusion in the use of terms designating workers in this field. At the time of World War I physiotherapy was the most familiar word, the technicians being known as physiotherapists. Later, the term physical therapy was more generally used, the doctor being designated as a physical-therapy physician, as distinguished from the physical-therapy technician. As the field broadened to include other types of treatment, such as occupational therapy and physical reconditioning, the technicians became known as physical therapists and occupational therapists, and the physician had no single term to indicate his specialty. The American Congress of Physical Medicine, the Society of Physical Medicine and the Council on Physical Medicine of the American Medical Association gave considerable thought to the coining of a suitable term to describe the specialist in physical medicine. The result of this is the word "physiatrist," which has now been quite generally accepted by those in the field of physical medicine but is still unfamiliar to the majority of physicians and laymen. This term is derived from the two Greek words "physis," meaning physical or natural, and "iatreia," meaning treatment.[1]

The need for a great many more physiatrists is easily understandable when one considers that they are responsible for the medical direction of rehabilitation programs in the Army, Navy and Veterans Administration, as well as of civilian hospitals, community rehabilitation centers and many industrial medical clinics. This development of medical rehabilitation, which is one of the most important aspects of physical medicine, is discussed in greater detail below.

The need for fundamental and clinical research has been recognized by many physicians, and the present status has been summarized in a previous paper of this series.[2] The report of the Baruch Committee on Physical Medicine emphasized the necessity of encouraging such research, and funds have been made available to aid scientists in this field. The work in the various centers devoted to research in physical medicine is still in its infancy but a few preliminary studies reported at the American Congress of Physical Medicine in September, 1946, are of interest.

There have been relatively few new developments in therapeutic technics in the past few years. Because of the interest in physical fitness in wartime, exercise therapy has received the attention of physiologists, psychiatrists and physical educationists, as well as that of the physiatrists. The results of some of their studies are reported below in the final section of this paper.

MILITARY REHABILITATION

Because of the acute manpower shortage occasioned by the war, the problem of returning injured workmen and service men to their former activities was attacked earlier in England than in this country. Since methods now being employed in this country are to a large extent adapted from those in use in England, it may be well to review briefly a recent paper by O'Malley[3] describing rehabilitation in the Royal Air Force. There is considerable misunderstanding about the meaning of rehabilitation, but this author states: "It denotes the restoration of the injured man to perform his duties — mentally, physically, socially, and technically — as efficiently as he did before he was injured. If we fail to make him equivalent, then he has to be resettled in another trade."

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The basic principles on which this plan of rehabilitation is organized are those of a system of restoration of mental and physical functions by physical and mental activity. It has been stressed that the art of rehabilitation is making the patient do his exercises regularly, efficiently and, above all, willingly, since there is no greater fatigue than that of boredom. The mental problem in rehabilitation is repeatedly emphasized. For this reason, it has been advocated that the center be functionally allied to hospitals, although geographically separate, so that the patient may be stimulated to self-endeavor in an atmosphere of enthusiasm coupled with a feeling of well-being, rather than the atmosphere of a hospital. It is taken for granted that there is continual progress and enthusiasm in such centers. O'Malley advocates a residential center accommodating 200 to 250 patients. Of the accommodations necessary beyond that of domestic facilities, first and foremost is a large gymnasium. In connection with this are the doctors' consulting rooms, secretaries' offices, cafeteria, physical-therapy rooms, swimming pool, rest rooms and sun terraces. Smaller gymnasiums are also advised for more individual treatment of patients with acute injuries. Outside the gymnasium there should be playing fields and also a library and other recreational facilities, such as a hall for dances, motion pictures, lectures, concerts and theatricals. Because the success of the work depends so much on the morale of both the staff and the patients, the right type of leadership and personality in the staff is stressed. Proper reception of the patients is thought to be of considerable importance on the principle "that if you want to keep a cat in the house you must butter its feet." Attempts at establishing a proper *esprit de corps* are begun at once.

The organization of the staff in this center consists of a commanding officer, or director, and three medical officers for each 250 patients. Under them are the physical-fitness officer and physical-training instructors, who are responsible for the exercise classes. The patients are classified according to injury groups, of which there are four main divisions — two in which the lower limbs are involved, and one each for injuries of the arms and spine — that, in turn, are graded according to degree of convalescence and ability to perform exercises. Physical therapists are used, but the emphasis is on exercise rather than on passive procedures, the early groups exercising first on the anatomic and later on the functional approach and finally for maximum efficiency. In the occupational-therapy section the work is partly diversional and partly remedial, aiming toward vocational training.

Remedial exercises have been divided into a direct and an indirect approach, the former comprising the exercises and treatments in the physiotherapy room, with a maximum time limit of about thirty minutes for this type of treatment, and the latter including swimming, cycling, clay-pigeon shooting, archery, roller skating, and games such as badminton and volley ball. The responsibility of grading, which is an important function, is left to the medical officer, since it has been found that premature removal of a patient into more advanced groups is as harmful as too prolonged periods in low groups.

The mental and social aspects are thought to comprise nearly 75 per cent of the problem, and the solution is afforded by the environment of the center and the personalities of the staff, as well as by a proper design for living — that is, a balanced program including light recreational activities together with more serious educational and vocational guidance.

The results of this program are of interest. In the unit reported by O'Malley approximately 10,000 injured persons were seen in a three-year period; 92 per cent of the injured air crews returned to duty, 64 per cent to the actual operation of flying, and 84 per cent of the technicians returned to their trade. In view of these results similar ventures are advocated for civilian life, and many of these are in actual operation.

Programs for convalescent care and rehabilitation in the Army Air Forces, Army and Navy have received considerable publicity in the medical and lay press.[4–11] The treatment for the convalescent patient starts while he is still in bed with physical reconditioning composed of short daily periods of light bed exercise designed to allay muscle atrophy in parts of the body not diseased or injured. At the same time educational reconditioning is begun, including organized lectures and group discussions. Thirdly, occupational therapy, consisting of light purposeful tasks, creative art or handicraft, such as leather working and wood carving, has been found of assistance in restoring function and is of benefit for morale. For ambulatory patients physical reconditioning is more strenuous, including calisthenics, gymnastics and athletic sports. At the same time the occupational therapy is graded for heavier work. Finally, physical training leads to conditioning for extreme physical exertion, and the educational retraining directs the patient by refresher courses in military training, including map reading, scouting, use of weapons and so forth. This educational retraining is adapted to the special needs of the patient.

Rehabilitation of Veterans

The rehabilitation of veterans is a problem of general interest, and the plans now in operation are worthy of more detailed consideration.[12, 13] The organization includes a central office in Washington in charge of physical medicine and medical rehabilitation that receives the advice of a national consultant. The country is then divided into branches roughly corresponding to the Army areas,

each with its own branch office and full-time physician in charge of physical medicine and medical rehabilitation. The branch areas similar to the central office have consultants, if possible, for physical medicine and rehabilitation in each area. Further subdivision is on the level of the hospitals, in which a chief of physical medicine is responsible for rehabilitation. Under him is an executive officer ordinarily with experience in rehabilitation in the Army or Navy. Technical services are divided into various categories, such as physical therapy, occupational therapy, physical reconditioning, educational retraining and shop retraining. The chief of physical medicine is responsible for prescribing treatment for patients in one or all of these sections, depending on individual physical and mental needs. Only physical and occupational therapists who are properly qualified may receive professional ratings and are given new appointments. Members of the technical staff in physical reconditioning, shop retraining and educational retraining are also required to have special qualifications by education and previous experience in these fields.

It is apparent that a more varied and graded treatment is available for convalescent patients in the Veterans Administration than in any civilian hospitals, with the possible exception of the better mental institutions. The success of this program can be achieved only when the entire medical staff is aware of its existence and cognizant of the proper selection of patients for referral. Plans have therefore been made to establish regular rehabilitation conferences of representatives of the various units mentioned above, together with social-service workers, psychiatrists, psychometrists and the ward officers, so that a total plan of rehabilitation can be mapped out for the patients. Further education of the general-hospital staff is provided by staff conferences and bulletins. Because the value of this rather elaborate and expensive setup for rehabilitation can be measured only by results, all the chiefs of physical medicine have been asked to devise new forms for recording progress and results. By this means new records now being distributed may, if properly utilized, help to evaluate the success of this important work.

The most rapid progress has been made in the mental institutions where the members of the staff are already familiar with many of the procedures of rehabilitation, such as shop work. The difference in the present goal, however, is that this type of therapy is aimed at directing the patient toward economic independence and complete social as well as physiologic recovery. Contacts with industry are therefore made, and already an appreciable number of patients have successfully taken their place in industry from mental hospitals as a direct result of this rehabilitation program.

At present, the plan of organization calls for physical and occupational therapy, physical reconditioning, shop retraining and educational retraining in the various types of hospitals, such as general medical and surgical, tuberculosis and neuropsychiatric. It is too early to determine exactly the significance of the treatment, but the physiatrists are doing clinical research to evaluate the results in the different types of hospital.

It is also the plan of the Veterans Administration to affiliate the hospitals whenever possible as teaching units of adjacent medical schools. This should be of benefit for the medical schools as well as for the Veterans hospitals, particularly in physical medicine, since the students will be able to see rehabilitation in action.

Civilian Rehabilitation

There is considerable statistical evidence that rehabilitation of industrial casualties and other civilians with physical handicaps is financially sound. In the relatively few cities in the United States where community rehabilitation centers are already established, much is being achieved by treatment of the injured patient during convalescence after the acute surgical stage, bringing him on to the point of re-employment. An apparent growth of social responsibility for the disabled is manifested by the Vocational Rehabilitation Act, which provides for the purchase of medical and surgical services for physical restoration of patients who may become employable by such treatment and are in financial need. There are, however, insufficient facilities at present to provide these services, since the average civilian hospital is not equipped to render treatment during the entire convalescent period because of lack of physical facilities and trained personnel. Physicians in general are little acquainted with the possibilities of such treatment and still refer patients to such facilities, even when available, only after months of ineffectual treatment. The medical schools, in general, are also doing nothing to train future physicians in this type of service.

Experience obtained from centers established in England and in the armed forces in the United States has made it possible to outline functional physical medicine and medical rehabilitation adaptable to civilian practice.[14–16] The first point is the introduction of physical reconditioning into every ward from the first stage of recovery from disease or injury, without allowing the patient the mental and physical deterioration from excessive inactivity. The second point is establishment of a plan of convalescence to speed recovery of physical and psychologic function. Thirdly, the form of treatment for rehabilitation must be adapted individually for the patient's disability as measured by careful functional tests. Another important point in the success of treatment is personal supervision by a properly trained physician through the entire program, that is, until the patient is placed in society and industry, when possible.

One of the simplest and most obvious means of combating disuse atrophy from bed rest has been the adoption of early rising following surgical procedures and in the puerperium. A number of reports on this subject have appeared in the literature, the consensus being that early rising is not dangerous but, in fact, reduces the incidence of complications, particularly those of thrombophlebitis and phlebothrombosis with pulmonary emboli. Convalescence is markedly speeded by this practice, which is of special value in these times of shortage of hospital beds.[17–22] In addition to early rising, leg exercises with special mechanical apparatus have been devised, particularly to reduce the incidence of pulmonary embolism secondary to venous thrombosis.[23] It has also been pointed out that simply getting the patient out of bed is not sufficient to protect against venous clotting, for to allow a patient to sit in a chair with the legs dependent causes greater circulatory stasis in the veins of the lower extremity than that produced if he contracts his musculature actively against resistance lying in the horizontal position. Early rising and ambulation, to be effective, require that the patient walk.[24]

The principle of separation of the rehabilitation from the hospital has been stressed in the armed forces for reasons of morale. As Hellebrandt[25] has pointed out, this separation is less urgent in civilian practice, where much may be gained by the close supervision of a resident medical staff if the rehabilitation section is connected with the hospital. A physical-medicine specialist in constant attendance is desirable for proper supervision of the treatment. Because of the tradition of not allowing patients to do things for themselves in general hospitals, some changes may be necessary in rehabilitation wards, as pointed out by Deaver.[17] He has emphasized the importance of functional education to teach fundamental activities and skills beginning with the most commonplace and humble acts. Patients such as paraplegics and hemiplegics may be graded according to their ability to perform the everyday activities of life, and simply by the act of grading performances their competitive spirit may be aroused, with the result that they are stimulated to more rapid recovery.

One of the most striking advances in rehabilitation concerns the treatment of patients paralyzed by injuries of the spine — that is, the paraplegic patients.[26–29] Special services to take care of these patients were developed in the armed forces, where the importance of teamwork was emphasized. The surgical care was handled by the neurosurgeon, orthopedic surgeon and urologic specialist. The patient must also be watched carefully for general nutrition by the medical specialist, and his skin taken care of by the nursing staff. With proper treatment it has been found possible to save the lives of paraplegic patients and, with the help of the medical-rehabilitation department, to teach the majority to be self-sufficient to a remarkable degree. Most of them can be taught to walk with crutches, even those with severe flexor spasms being relieved by anterior rhizotomy.[30] Compensatory development of the upper extremities, under the supervision of physical rehabilitationists, aids the patient in learning to walk under the direction of a physical therapist. Skills are developed first by the occupational therapist, and later in the shop retraining department, so that actual vocational training is achieved. Contacts with industry have been made in many of the hospitals so that patients may be gainfully employed while still in the hospital and on discharge. Morale has been fortified by grouping patients with similar injuries in centers where improvement is placed on a competitive basis, including individual scoring systems.

Centers have also been admirably developed for the care of amputees. Again, general physical development is stressed, and proper use of prostheses taught, including ambulation and vocational training.[31] There are, however, many more amputees in civilian practice than resulted from war injuries, and the fine results achieved in service hospitals remain as a challenge for better treatment in civilian practice.

New Technics

In view of the considerable emphasis on rehabilitation, particularly early return of function in diseased and injured extremities, it is understandable that the greatest interest in physical-therapy technics has recently concerned exercise therapy. The method that has perhaps attracted the most attention is that of systematized weight lifting adapted to therapeutic exercise. DeLorme[32] developed in the Army a program of heavy-resistance, low-repetition exercise based on the technic of weight lifters. This was found to be extremely effective in developing muscle strength following traumatic lesions of the bones, joints and surrounding tissues. This system of training can be briefly summarized as follows: individual exercises with a load heavy enough to preclude more than ten to fifteen successive contractions; an increase in resistance as soon as the load can be lifted ten consecutive times with ease; periodic attempts to surpass and improve the maximum performance; and rest periods in relation to the day of maximum performance for testing.

Applying these principles of weight lifting, DeLorme devised an apparatus that was mechanically suitable for exercising all the major muscle groups of the trunk and extremities. He reported signal success in increasing strength of the muscle groups so exercised, together with actual hypertrophy as judged by circumferential measurements.

It is well known that such methods, although empiric in origin, are successful in developing the strength of normal persons. Some investigations to explain these results have been made by Houtz

et al.[33] from tests on normal control subjects. The conclusions, in part, were as follows:

> The most important single element in the intensification of the daily volitional work output is the will to perform with physiologically maximum effort. Augmentation in strength through daily exercise is associated with significant increase in the work done on the limit day. The rate of improvement in work capacity is rapid under a program of heavy resistance exercise. Strength may more than double in four weeks with systematic training. There is no evidence of significant loss in the kind of increase in work capacity which is acquired by heavy resistance exercise during the post-exercise period which exceeds in duration the initial period of training. The ability to perform work may continue to improve after the cessation of systematic training. This phenomenon suggests changes of an unexplained kind associated with motor learning among which must be included significant extension of the psychological end point of fatigue.

In view of these early reports of success in this method of exercise therapy, a study of its use in various pathologic conditions is warranted. Its possible value in the treatment of poliomyelitis is at present being studied.

Other specialized exercise technics have been developed in the therapy of diseases of special parts of the body. For example, systematic preoperative and postoperative exercises have been found to be of value for patients subjected to chest surgery, particularly thoracoplasty. The greatest success is obtained when exercises are started preoperatively with explanations to the patient of what his postoperative problems will be. These include the mobility of the shoulder and scapula and the function of the supporting musculature of these parts, proper breathing and posture. Actual details of procedures to be used have been reported by several authors.[34–36]

Correct posture and body mechanics has continued to receive the interest of orthopedists and physical therapists, particularly because of its preventive implications.[37] Quantitative methods of evaluation have been described.[38] The dynamics of posture have been emphasized by Howorth.[39] He pointed out the changes during infancy, childhood and adult life and the variations in sitting, standing and lying positions that are generally encountered. The advantage of good basic dynamic position is stressed in athletics as well as in everyday life, and the acquisition of such control is thought to be rewarding in the reduction of fatigue, avoidance of accidents and even as an "approach to life."

One aspect of therapeutic exercise is instruction of patients in the use of crutches. Although the usefulness of these aids to ambulation is generally accepted, little information is readily available in the literature for instruction of students, physical therapists, patients or physicians. Deaver and his associates[40, 41] have recently published detailed articles with illustrations showing the proper use of crutches for various conditions. These papers have also been reprinted in a monograph that is a definite contribution to the literature of physical medicine.

Combined Drug and Physical Therapy

Other procedures in physical medicine that have received considerable attention include the combined use of certain drugs that have an effect on neuromuscular function and exercise therapy. Curare, which is known to have an inhibitory effect on neuromuscular transmission, has been used to reduce spasticity in central-nervous-system diseases, such as hemiplegia and infantile cerebral palsy. To provide for prolonged effect a suspension of curare in a mixture of peanut oil and wax has been said to provide relaxation of muscle spasm up to three days' duration.[42, 43] With such a method of administration the unpleasant side effects were absent. Maximum benefit from the drug was obtained when physical therapy was also administered to increase function when spasticity was reduced. This combination of curare and therapeutic exercise, according to Schlesinger,[42, 43] is most effective in cases in which some voluntary function is present, rather than in paraplegic patients with spasticity and no active motion.

Schlesinger and Ragan[44] have also reported beneficial effects from curare in the treatment of muscle spasm of other origin, particularly that associated with acute low-back pain. Jones[45] states that curare may be used to help in the differential diagnosis of muscle spasm of reflex origin from that due to organic changes in limitation of passive motion or in the joints. It has also been suggested that curare is of value in the differentiation of pain due to nerve-root irritation and that secondary to inflammation of joints and surrounding tissue; the former is not affected by curare, and the latter is relieved. Although considerable lay excitement has been instigated by reports of remarkable success from this combination of curare and physical therapy in the treatment of spastic conditions, in my opinion its true worth will be known only after careful clinical analysis. Almost all patients who have previously had little or no treatment are benefited when given systematic physical therapy, particularly when their hopes are keyed up so that co-operation in the program is good. Just how much of the success of treatment is dependent on curare and how much on the physical therapy and how much is due to the combination will be known when more complete reports are published.

Curare has also been used in the treatment of infantile paralysis in a few clinics, with conflicting reports.[46, 47] The rationale of using a drug that is known to cause loss of voluntary muscle control in a disease that causes flaccid paralysis of muscles is not apparent to most physicians. Although it may be possible to relieve meningismus and other types of muscle hyperirritability present in the acute stage,

its value in reducing residual paralysis can be determined only by further study.

Neostigmine (prostigmine) is another drug that has recently received a great deal of publicity because of reported benefits in relieving muscle spasm, particularly when combined with the usual types of physical therapy. There can be no doubt that this drug acts to stimulate the intestinal tract and has striking clinical beneficial effects in relief of the symptoms of myasthenia gravis. The increase of muscle strength, which is striking in these patients, is thought to be due to the inhibition of cholinesterase, which is the agent destroying acetylcholine, an important factor in neuromuscular transmission. The action is primarily at the myoneural junction, but there is some evidence of effects in spinal centers, particularly relief of spasticity in patients with spinal-cord disease or hemiplegia. This drug has accordingly been tried in a wide variety of diseases in which there is evidence of muscular spasm, spasticity, cramps or pain. One group has reported beneficial results in poliomyelitis, rheumatoid arthritis, cerebral palsy, hemiplegia, facial paralysis, subacromial bursitis and similar conditions as judged by clinical response, together with the use of physical therapy.[48, 49] Clinical appraisal of beneficial results seems to be lacking in the early reports, and, as is often true, later studies are beginning to show negative results — for example, in the treatment of rheumatoid arthritis.[50]

Research

Fitness Tests

Although research in physical medicine has recently been reviewed, the increasing emphasis on exercise therapy justifies a summary of some of the latest studies on testing physical fitness. Physical-training programs were developed to a remarkable degree during the war with the hope of increasing capacity for physical exertion and also efficiency in activities not requiring much physical exertion, such as piloting aircraft. To assess the value of these programs it is necessary to develop methods of measuring physical fitness. This subject has been reviewed by Johnson,[51] of the Harvard Fatigue Laboratory. He has pointed out that if unquestionably fit and unfit men of similar stature are compared while performing the same work, which they are able to sustain in a steady state, the fit men show a greater oxygen consumption, a slower pulse rate, a lower systolic blood pressure, a larger stroke volume and a lower blood lactate during work and a faster return of the blood pressure and pulse rate to resting value after work. If the work is too much to be maintained steadily, the fit man shows a longer duration of effort before exhaustion, a higher oxygen consumption, a somewhat slower maximal pulse rate, a larger stroke volume, a higher blood lactate and a faster return of the blood pressure to normal after work. In other words, the man who was said to be fit carries on moderate work with less disturbance of physiologic equilibrium. When forced, he can displace this equilibrium farther and for a longer time, and his recuperative powers are such that after exhausting exercise he returns to normal more quickly.

The physical-fitness tests most widely used tax the cardiovascular system by exercises involving large muscle groups without demanding unusual types of skill, as in the step test, treadmill and bicycle ergometer.[52, 53] The most frequent measurements are oxygen consumption, pulse rate, blood pressure and blood lactate. An important difficulty in all such measurements is that the patient must have motivation to do well. The ideal test would therefore eliminate the psychologic factor. These tests have been used fairly successfully in the measurement of physical conditions before and after periods of training. The conclusions from these studies are that it is impossible at present to predict by a single examination how much a given subject is capable of improving with training and that men in reasonably good condition at the start of the program require more vigorous training to improve significantly than men in poor condition.[54]

Significant clinical applications of these physical-fitness tests have been made in progress of rehabilitation and convalescence. Landis[55] has pointed out the value of adjustment to the peripheral circulation encountered during convalescence. His physiologic analysis gives weight to the importance of early supervised exercises performed by patients while still in bed, followed by more active physical reconditioning during convalescence. Karpovich, Starr and Weiss[56] reported speeded convalescence by physical-training programs during which the degree of activity was determined by graded step tests. Physical-fitness tests have also been used in studies of neurocirculatory asthenia, effort syndrome and fatigue states. During exercise on the bicycle ergometer it has been found by some workers that there was a significantly poor exercise response in the psychoneurotic patients as compared with normal controls.[57] Oxygen uptake, lactate rise and pulse rate were determined, and oxygen consumption was considered the most satisfactory quantitation of exercise response. Cohen et al.[58] observed abnormally small displacement of homeostasis with maximal effort and abnormally large displacement with moderate work, indicating poor physical condition. They suggested that this intolerance to effort was due to constitutional inferiority. Both psychologic and physiologic studies in psychoneurotic patients complaining chiefly of fatigue were carried out by Watkins and his associates,[59] who noted that certain psychologic states seemed to precipitate or consistently preceded the onset of fatigue. In the same group of patients submaximal work on the bicycle ergometer was accompanied by abnormally high lactate values that may have indicated poor

physical fitness, and there was similarly a higher increase in lactate following a grip test, with an output of more electric discharges from the muscles when measured electromyographically.

The search for improvements in measurements of fitness still continues, one of the most recent being based on the change in the reduction time of blood after breath holding.[60] Others have emphasized the value of skill and the psychologic factors in evaluating working capacity, particularly of the physically impaired. Such measurements are essential to the successful working of rehabilitation programs resulting in correct placement in industry.[61–63]

Electrophysiology

Studies are still reported on technics of electric stimulation and the effects of such stimulation on atrophy of denervation and disuse. Many different wave forms have been used for stimulating nerve and muscle, such as the sine wave, exponentially following currents, inductive impulses and square waves. Offner[64] calculated on the basis of heat production that that wave form causing excitation with minimum injury was an exponentially rising current. Because such a current is not readily produced by simple electronic circuits, the next best wave form for clinical use is the square wave, sine waves being the least efficient, requiring 85 per cent more power than the most efficient type.

Fischer and Ramsey[65] found that daily electric stimulation of denervated rabbit muscle was effective in retarding weight loss and deterioration of muscle protein. Treatment applied against high resistance was more effective than when the muscle contracted freely or against little resistance. A study of protein concentration and atrophy due to tenotomy disclosed that the changes were practically the same as those following denervation.[66] The atrophy of demobilization alone was nearly as great as that from the other two conditions, but the total protein concentration loss was only about a third. Kosman, Osborne and Ivy[67] also found that appropriate electric stimulation favorably altered the course of degeneration after crushing of the sciatic nerve in rats. Young[68] reported that muscle atrophy developed in the absence of either stimulation from above or resistance from below, both factors being essential for hypertrophy. Massage of denervated muscle, according to Suskind et al.,[69] caused only slight retardation of weight loss but was effective in maintaining the strength. Electric stimulation retarded weight loss but exerted no effect on the contractible strength per unit mass of muscle. It was concluded that effective therapy for treatment of paralyzed muscles is a combination of electric stimulation and massage.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 33211

PRESENTATION OF CASE

A forty-six-year-old restaurant manager entered the hospital because of dyspnea and swelling of the ankles.

The patient had been well until two and a half years before admission, when he suffered from the gradual onset of marked dyspnea, moderate ankle edema, easy fatigability, orthopnea and attacks of nocturnal dyspnea. After six months he consulted a physician, and under bed rest, digitalis and intravenous diuretics the symptoms subsided. Five weeks later he resumed work but continued to have moderate dyspnea without ankle swelling until four months before entry, when all the former symptoms gradually returned. He was, however, able to continue his job until a month before admission, when the symptoms became so severe as to force him to bed. Brief attacks of nocturnal breathlessness occurred almost every night. The edema failed to disappear on bed rest, but never extended above the ankles. The patient became extremely anorexic, was unable to sleep well and needed three or four pillows. Over a two-year period there had been occasional episodes of coughing productive of yellow mucus, with moderate exacerbation in the last month. There was no history suggesting rheumatic fever, syphilis or hypertension.

Physical examination disclosed a patient who was sitting in bed in slight respiratory distress and coughing frequently and forcefully. The lungs were resonant and clear. The cardiac border extended to the anterior axillary line in the seventh intercostal space. Thrills were palpable at the apex and in the third and fourth interspace to the left and right of the sternum. A high-pitched Grade IV systolic murmur, followed by a low, rumbling diastolic murmur, was audible at the apex. Along the left sternal border there was a harsh Grade IV systolic and a loud, high-pitched diastolic murmur. The rhythm was regular, and the rate 75 per minute. The liver edge extended 3 cm. below the right costal margin and was tender and firm. The spleen was not palpable. There was moderate edema over the lower portion of the back and marked edema of the legs. The feet were warm.

The temperature was 98°F., the pulse 76, and the respirations 16. The blood pressure was 106 systolic, 80 diastolic.

Examination of the blood revealed a red-cell count of 4,300,000, with a hemoglobin of 13.8 gm. per 100 cc., and a white-cell count of 12,500, with 74 per cent neutrophils. The urine gave a ++ test for albumin; the sediment contained an occasional white cell only. The nonprotein nitrogen was 45 mg., the fasting blood sugar 95 mg. and the total protein 5.4 gm. per 100 cc.

Treatment consisted only of bed rest, mild sedation, ammonium chloride and continuance of digitalis. During the second night in the hospital the patient was unusually restless. The next morning he looked poorly; he was sweating profusely and felt weak. Physical examination revealed no change except that the pulse was totally irregular and the blood pressure was 112 systolic, 102 diastolic. Two or three minutes after being examined the patient

suddenly had a tonic convulsion and died. On application of a stethoscope to the chest within thirty seconds after the onset of the convulsion no heart sounds could be heard.

Differential Diagnosis

Dr. Sylvester McGinn: It seems to me that the diagnosis in this case revolves around an interpretation of the thrills and the murmurs. As the heart sounds are recorded in this abstract considerable desirable information is lacking. For instance, I should like to know about the pulmonic second sound and whether or not it was accentuated enough to suggest pulmonary regurgitation.

Dr. Tracy B. Mallory: I carefully looked through the record for that information but could not find it.

Dr. McGinn: I should like to know about the timing of the thrills.

Dr. Mallory: Can you answer any of these questions, Dr. Bland?

Dr. Edward F. Bland: No.

Dr. McGinn: Cyanosis is not mentioned; I assume that it was not observed. A productive cough had been present for two years, but there is no record of a sputum examination, which I again assume was not done. The x-ray studies might be helpful, and the cardiologist finds some solace in electrocardiograms. I am sure that electrocardiograms were not taken, since we are not given that information. I should like to know the albumin-globulin ratio. Occasionally, with edema of the lower legs, lipoid nephrosis is present. In this case the urine showed a ++ test for albumin, but I think that we have other information that will probably account for the diagnosis without the several things that I have made reference to. It is apparent that left and right ventricular failure was present, the cardiac asthma and nocturnal dyspnea being indicative of weakness of the left side of the heart and the engorged liver and the edema being indicative of right heart failure. Constrictive pericarditis could give the appearance of right ventricular failure, but in that condition the patient is usually not orthopneic; on that basis I believe that this diagnosis can be excluded.

Thrills may be due to valvular heart disease or congenital lesions and sometimes occur with acute dilatation of the heart. Acute dilatation can be due to acute rheumatic myocarditis or adhesive pericarditis or may represent the dilatation that is terminal in a large hypertrophied heart. It is difficult to believe that it was present in this case with a pulse rate of only 75. The temperature was normal. I think that there was something beyond acute dilatation to explain the thrills.

There are several kinds of systolic thrills, but when a thrill is maximal in the third or fourth interspaces, one thinks first of a congenital anomaly such as Roger's disease or an interventricular septal defect; in such cases, however, the heart is usually small. The heart in this case was large. The location of the thrill could go with a pulmonary stenosis. In pulmonary stenosis the thrill is generally felt in the second left interspace, and in most cases of pulmonary stenosis cyanosis is such a marked feature that it is included in the record of the examination. The thrill of aortic stenosis in the early stage is located in the second right interspace as a rule, but as cardiac hypertrophy progresses it is possible for the thrill and the murmur to be displaced downward, even to the third and fourth interspaces. The thrills in this case were not timed, but the most frequent apical thrill is the diastolic thrill of mitral stenosis. Occasionally, diastolic thrills occur at the left sternal border, but if so they are due to rupture of the aortic-valve cusps, a rare condition. The description of the murmurs at the apex in this case report signifies mitral regurgitation and mitral stenosis, and I think that they must be accepted as such. We must account for systolic and diastolic murmurs at the left sternal border, which might have been due either to pulmonary stenosis with regurgitation or to aortic stenosis with regurgitation, probably the latter. There is no indication that the systolic murmur was transmitted to the neck; I think that that finding would tend to clinch this diagnosis. Left ventricular failure is evidenced by the history of cardiac asthma, and right ventricular failure by liver enlargement. The statement that the cardiac border was in the seventh interspace at the anterior axillary line indicates an extremely large heart. Death was apparently primarily cardiac. I do not believe that it was embolic. The heart sounds were inaudible when the patient was examined within thirty seconds after death. The arrhythmia that preceded the exitus was probably due to coronary insufficiency and ventricular fibrillation. The possibility of a pulmonary embolus in congestive heart failure is great. It is my impression that the outstanding lesion in this case was aortic stenosis of high grade and with calcification of the valve. The location of the murmur and the thrill bears this out, as does the small pulse pressure, the low blood pressure and the regular rhythm. Patients with mitral stenosis in congestive failure are usually fibrillating, unless some other lesion is predominating.

Finally, we must consider the mode of death. Patients with aortic stenosis often die suddenly. I do not know whether or not there was interference with the coronary circulation.

Clinical Diagnoses

Rheumatic heart disease.
Aortic stenosis and regurgitation.
Mitral regurgitation and (?) stenosis.
Congestive failure.

Dr. McGinn's Diagnoses

Rheumatic heart disease.
Aortic stenosis and regurgitation, with calcification.

Mitral stenosis and regurgitation.
Cardiac hypertrophy.
Congestive failure, left and right ventricles.

Anatomical Diagnoses

Calcareous aortic stenosis.
Congenital bicuspid aortic valve.
Hypertrophy of left ventricle, marked.
Deviation of interventricular septum: ? Bernheim syndrome.
Mural thrombi, left and right auricles.
Pulmonary embolus, small, left upper lobe.
Chronic passive congestion, lungs, liver and spleen.
Pancreatitis, chronic, of moderate severity.

Pathological Discussion

Dr. Mallory: Autopsy showed an extremely hypertrophied heart, the cause of which was an obviously stenotic aortic valve (Fig. 1). It appeared to have only two cusps, both of which were massively calcified, and there were great warty excrescences of calcium in the sinuses of Valsalva. Each of these cusps appeared considerably larger than a normal cusp. On one side I think that a ridge could be made out in the middle of the cusp, such as that seen in congenital fusion of the aortic valve. It is my impression that a large proportion of these calcareous aortic stenoses develop on the basis of congenital bicuspid valves, and this case suggests that etiology.

Dr. Walter Bauer: What do you mean by a large percentage — 20 or 80 per cent?

Dr. Mallory: Eighty per cent.

Some difference of opinion was expressed regarding the mitral valve. I thought that it was normal, without evidence of rheumatic heart disease. The coronary arteries showed minimal atheromatosis. The left ventricle was particularly hypertrophied (Fig. 2), and the right ventricle was reduced to a rather narrow slit. This suggested the possibility of a Bernheim syndrome, if one believes in such a thing, and I should like to raise that point for discussion. To those not familiar with the hypothesis, Bernheim[1] suggested many years ago that in certain cases of massive dilatation or hypertrophy of the left ventricle, deviation of the septum into the right ventricle produced sufficient narrowing of the right ventricle so that it was unable to fill properly with blood and failure of the right side of the heart occurred secondary to left ventricular hypertrophy.

Have you any comment, Dr. Bland?

Dr. Bland: I have never recognized this syndrome clinically. Once or twice a year someone from the Pathology Department presents us with a possible example post mortem. It is an interesting concept. It implies not exactly right-sided heart failure but rather an inability of the blood to get into the right ventricle. In 1945, 3 cases that clinically fit in more or less with this concept were described.[2] The patients were said to have had right-sided heart failure, swelling and edema, without previous pulmonary congestion (left-sided heart failure), and at post mortem the sections were similar to the one that Dr. Mallory has just demonstrated.

Dr. Mallory: Those who believe in the syndrome consider the diagnosis to require evidence of right-

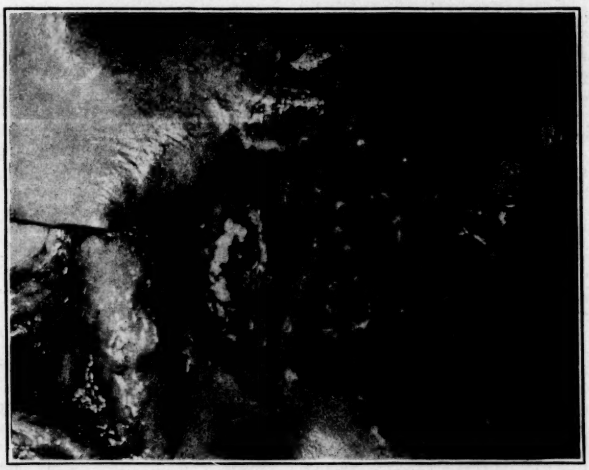

Figure 1. *Photograph of the Aortic Valve.*

sided heart failure before evidence of left-sided heart failure. In most published cases evidence of such a sequence is sketchy, as in the case under discussion. This man had paroxysmal dyspnea, probably due to left ventricular failure at an early stage in the symptoms.

DR. BLAND: I wonder if that concept need be true. It takes time for the left ventricle to encroach by hypertrophy or dilatation into the right ventricular cavity. May it not be failing at that time, whereas later on it actually obstructs the inflow into the right ventricle and the signs of right-sided heart failure intervene?

DR. MCGINN: This is an early age for occurrence and an unusual period for a patient with aortic

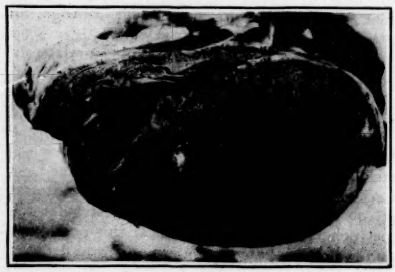

FIGURE 2. *Photograph of a Cross Section of the Heart.*

stenosis to survive in congestive failure unless explained by a damaged myocardium or by the Bernheim theory.

DR. MALLORY: The patient died at an early age for calcareous stenosis — fifteen years younger than the average.

DR. MCGINN: When congestive failure appears with aortic stenosis there is usually a downhill course over a period of seven or eight months. I believe that this case was complicated either by myocardial changes or by a Bernheim syndrome.

DR. BAUER: This case may have been the exception.

DR. MALLORY: Yes.

DR. MCGINN: In answer to the question about the mitral murmurs, it is possible for a dilated heart to give the findings of mitral stenosis with a typical murmur and thrill in the presence of a normal valve. It is interesting that in this case the maximal location of the aortic-valve murmur and thrill was in the third and fourth interspaces.

A PHYSICIAN: Have you seen any cases of the presystolic crescendo that turned out to have a normal mitral valve?

DR. MCGINN: I recall a case that seemed to be so typical that a valvulotomy was done.

A PHYSICIAN: What do you consider the cause of death in the case under discussion?

DR. MALLORY: No anatomic immediate cause of death was found. I think that one must assume that it was due to ventricular fibrillation.

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CASE 33212

PRESENTATION OF CASE

A fifty-eight-year-old Polish mill worker entered the hospital because of hematuria.

Ten months before admission there had been a single episode of painless massive hematuria. Three months later hematuria began intermittently, and gradually became more frequent and severer so that by the week before entry the patient was passing "jelly-like" urine. No symptoms attended this bleeding until two days before admission, when there was mild left-flank discomfort.

The patient had had a chronic cough for years, but there was no history of tuberculosis or other major illness.

Physical examination disclosed persistent moist rales at both lung bases. The heart and abdomen were normal. There was no costovertebral-angle tenderness. Rectal examination revealed the prostate to be enlarged two and a half times normal, soft, smooth and symmetrical, and a sessile mass, about 3 cm. in diameter, was palpated high in the posterior rectal wall. A cystoscope was passed easily. There was a long, worm-like clot lying unattached in the floor of the bladder. The mucosa was normal, and the capacity 300 cc. The trigone and ureteral orifices looked normal. Clear urine was ejected from the right ureter; none from the left. There was mild hypoplasia of the median and lateral lobes of the prostate; the prostatic urethra appeared normal. Catheters were passed to 28 cm. on both sides, a slight obstruction being felt at 25 cm. on the left. Bloody fluid was aspirated from the left ureter, although there seemed to be no actual production of urine on that side. A smear of this fluid prepared according to the Papanicolaou technic showed tumor cells. Indigo-carmine appeared on the right two and a half minutes after injection; none was seen on the left.

The temperature was 99°F., the pulse 88, and the respirations 22. The blood pressure was 180 systolic, 100 diastolic.

Examination of the blood revealed a red-cell count of 4,650,000, with a hemoglobin of 85 per cent, and a white-cell count of 11,200. The urine had a specific gravity of 1.014 and gave a +++ test for albumin. Urine culture revealed no growth. The sediment contained innumerable red cells. The total protein, nonprotein nitrogen, carbon dioxide and chloride were normal.

An intravenous pyelogram showed normal function on the right, but none on the left. A retrograde pyelogram demonstrated markedly dilated calyxes in the lower portion of the left kidney; no calyxes filled in the upper portion. The ureter was not outlined, but the ureteropelvic insertion appeared to be low. X-ray films of the skull and spine showed no evidence of tumor. Biopsy of the rectal mass showed adenocarcinoma.

A renal operation was performed on the sixth hospital day.

Differential Diagnosis

Dr. Archie L. Dean*: The history suggests organic disease somewhere in the genitourinary organs, and the painless massive hematuria suggests that it came from one of the kidneys. "Massive" seems to be the term to use in this case. I think that the term "total hematuria" is a good one too, indicating that the blood is diffused equally throughout all the urine, in contradistinction to initial or terminal hematuria. That is one of the characteristics of bleeding from the kidney. It should be emphasized that the hematuria, no matter what the cause, was always intermittent in this case.

I assume that the sessile mass in the wall of the rectum represented a carcinoma of the rectum.

"There was a long, worm-like clot lying unattached in the floor of the bladder." That also helps to localize the source of the bleeding in one of the kidneys, because not infrequently if the kidney bleeding is sufficiently severe so that clots form, a perfect cast of the ureter is passed.

"Clear urine was ejected from the right ureter; none from the left." This was at a time of bleeding so that we are assisted to a certain extent in localizing this hemorrhage in the left kidney or ureter.

After referring several hundreds of specimens to Dr. Papanicolaou while he was developing his technic, I can state that a definitely positive diagnosis is of considerable clinical significance. By the use of this technic, however, one would not expect to be able to differentiate a tumor of the renal pelvis from a tumor of the renal parenchyma that had ulcerated into the pelvis.

"Indigo-carmine appeared on the right two and a half minutes after injection; none was seen on the left." That may or may not have significance in relation to the hypertension, on the basis of obstruction of the vascular system of the left kidney.

The x-ray appearance could have been due to a tumor of the parenchyma, with obliteration of the upper calyxes. It could also have been caused by tumor of the pelvis. It is less likely that it was due merely to a clot.

The ureter was not outlined, but the ureteropelvic insertion appeared to be low — there may be significance to the word "low," but I do not believe that it is of primary importance.

*Associate professor of urology, Cornell University Medical College, New York City.

There is no mention of a film of the chest; I should like to see one.

Biopsy of the rectal mass showed adenocarcinoma. Since the most frequent type of tumor of the renal parenchyma is an adenocarcinoma, one wonders if there was an association. I think that such an association is extremely rare, although multiple tumors are quite common. But either a primary adenocarcinoma of the kidney giving rise to metastases in the rectum or a rectal tumor involving the kidney is too rare to be considered seriously.

Dr. Laurence L. Robbins: A film of the chest was taken, and so far as I can see, the chest is entirely normal. There is no evidence of tumor. The changes in the heart and aorta are what one would expect in a man of this age. The lungs are essentially clear.

The pyelograms are essentially as described in the protocol. In the intravenous pyelogram there is no evidence of function on the left side over a relatively limited period. The right urinary passages are, so far as I can see, normal. This is a film of a retrograde pyelogram. On the left side we see filling of the inferior calyxes, which are dilated, with some irregularity along this area. The ureteropelvic insertion appears to be lower than is usual. At no time do we see a good kidney outline, other than the lower pole, on the left side. This film suggests that the upper pole is somewhat widened at this point, but I do not believe that the film is sufficiently detailed to be certain.

Dr. Dean: This appears to be a pyelogram of a tumor of the upper pole of the kidney, obliterating the upper calyxes.

A Physician: Could it not be a double kidney?

Dr. Dean: It could be, although it does not look just right for that.

Another point is that there is usually some degree of function in a kidney that has a tumor limited to the upper pole. The lack of function is something that I have not been able to understand. I am uncertain because the picture is not clear cut. But on the basis of the findings, the best I can suggest is a tumor of the upper pole of the left kidney.

A Physician: I should like to ask if Dr. Robbins can recognize the outline of a mass on the left. From where I sit I can see a definite shadow.

Dr. Robbins: So far as I can tell the mass to which you refer is produced simply by the colon swinging around in this manner. This other mass, of course, is fluid in the fundus of the stomach, which disappears as soon as the patient is turned over on the abdomen, when it is replaced with air. The thing that is bothersome is that it is not possible to see a definite mass in the region of the upper pole of the kidney.

A Physician: Do we have any information about the differential count? The white-cell count was 11,200, but no differential is given.

Dr. Fletcher H. Colby: It was normal.

DR. TRACY B. MALLORY: Dr. Chute, will you tell us the operative findings?

DR. RICHARD CHUTE: I helped Dr. Rogers, the resident, do the operation. The lesion turned out to be a papillary tumor of the kidney, which was removed by transperitoneal nephrectomy. The kidney was approximately normal in size. There was papillomatosis of the renal pelvis, which was much more marked in the upper pole than in the lower pole. The upper calyxes were entirely filled with tumor, whereas in the lower ones there was a considerable amount of space that the retrograde dye could not enter.

DR. COLBY: What was the preoperative diagnosis?

DR. CHUTE: Tumor of the kidney.

A PHYSICIAN: Was there any drop in blood pressure after operation?

DR. MALLORY: Nothing to suggest shock.

A PHYSICIAN: Was not the diagnosis of tumor made on interpretation of the pyelogram?

DR. COLBY: I think that in this case we paid a good deal of attention to the tumor cells. Is that true, Dr. Chute?

DR. CHUTE: The pyelogram offered one bit of contributory evidence, but we were not swayed by that.

DR. COLBY: I was interested in Dr. Dean's remark regarding Dr. Papanicolaou's technic, because we are now going through the throes of trying to evaluate the smear diagnosis of carcinoma in cases such as this. We are not yet certain about this test. In one case we got a positive report of tumor cells, and since there was a definite renal defect on x-ray examination, the kidney was removed; but no tumor was present anywhere in the kidney. That set us back on our heels a good deal. The disturbing thing was that the slide that contained the tumor cells was broken, so that we were unable to check it. We believe that the presence of tumor cells in the urine is not sufficient justification for removing a kidney. This test is still in the experimental stage, and we do not wish to decry the procedure on one unfortunate experience. Everyone, including the X-ray Department, thought that we were justified in operating on the patient regardless of the presence or absence of the tumor cells in the urine.

DR. DEAN: There are two conditions that we know of in which tumor-like cells can be found and one would not wish to remove the kidney. One is adenoma of an exceedingly low grade of malignancy. The other is ureteritis cystica. The cells from the surfaces of the small cysts look like those of a papilloma.

DR. DAVID W. WILLIAMS: In our experience in a series of 100 consecutive cases there were positive reports in 8, and 7 of these patients were proved to have tumors. One out of every 8, in other words, is an error.

DR. MALLORY: The same diagnostic problem of the value of smear diagnosis of cancer, of course, holds for cancer of the female genital tract and of the lung. There are cases in which it is impossible to obtain a biopsy specimen and in which smear examination has led to a positive diagnosis. For instance, cancer of the fallopian tube has been correctly diagnosed on smear. In the lung it is not uncommon to have a tumor so far out in the periphery that it is impossible to reach it with a bronchoscope. We believe that a positive smear constitutes important evidence. We are still conservative, however, in accepting it without other support, and if there is any chance of confirming the diagnosis with biopsy of the old-fashioned sort, we always do it.

A PHYSICIAN: How much better are aspiration biopsies than the Papanicolaou technic?

DR. MALLORY: That depends entirely on who takes the biopsy. There is in my experience about one surgeon in twenty who can take satisfactory aspiration biopsies. The rest are not worth looking at. It seems like a simple technic, but most people are not successful in providing anything on which I can make a diagnosis.

A PHYSICIAN: Are the successful surgeons consistent?

DR. MALLORY: Yes, most of them have learned the technic elsewhere — in Stockholm or at the Memorial Hospital in New York.

CLINICAL DIAGNOSIS

Renal tumor.

DR. DEAN'S DIAGNOSIS

Tumor of upper pole of left kidney.

ANATOMICAL DIAGNOSIS

Papillary carcinoma of left renal pelvis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The real question came up in the later handling of this patient with a papillary tumor of the renal pelvis. One knows the possibility of recurrence of such a tumor, whether by implantation or not, farther down in the ureter and sometimes in the bladder. This man had a simultaneous carcinoma of the rectum, and he eventually went through three operations.

DR. COLBY: One question that came up was whether it was advisable to remove the entire ureter, since the patient had another cancer.

DR. MALLORY: I think that the cancer of the rectum was far more important than the possibility of cancer of the ureter.

A PHYSICIAN: It is easy to take out the stump of the ureter when the rectum is removed.

DR. MALLORY: I should think that would be the best procedure in such circumstances.

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NEW YORK ACADEMY OF MEDICINE

The autumn that saw the first public demonstration of ether as an anesthetic also witnessed another event less spectacular in its nature and less far-reaching in its influence, but still of continuing importance to the progress of medicine. This event was the annual meeting, at Peletier's Restaurant, on Broadway, New York City, of the Society for the Relief of Widows and Orphans of Medical Men. The importance of this particular meeting, a century ago, was that from it came the preliminary plans for the establishment of the New York Academy of Medicine.

The original function of the Academy, according to its story as told by Dr. Howard A. Rusk, in the March 9 issue of the *New York Times*, was "to promote the honor, dignity, the respectability and the usefulness of the medical profession." That function has not changed, and the distinction with which it has been discharged has increased as the years have rolled on, even until this, the year when its centennial celebration has recently been observed.

Important among the various functions of the Academy has been the maintenance of its library, coeval with the Academy itself, and now numbering 225,000 volumes, a library second in size only to the Army Medical Library in Washington. The Academy has also put on foot various studies contributing to the public health and to the practice of medicine; under its auspices are conducted public lectures on health and disease, similar to those sponsored in this city by the Harvard Medical School.

Various associations brought deliberately into being for the unselfish motive of improving the welfare of mankind have had long and inspiring histories. Such organizations have been the English and Scottish Royal Colleges of Physicians and Surgeons, dating back to the sixteenth century, and their American counterparts, as well as the Royal Society of London — the "Invisible College" — that rose, with others, in the seventeenth century. There have been many such associations, first and last, for the promotion of science in general and a better understanding of disease in particular, for "where there is love of man there is love of the art."

There is, curiously, no similar organization in New England, although the various functions of an academy are adequately carried on by the state medical societies, the medical schools and, notably, the Boston Medical Library, fellowship in which carries with it a dignity and an intellectual prestige that still have their value.

MALNUTRITION AND GROWTH

Certain phenomena that have been observed in relation to growth in the human species deserve our attention. In a matter of generations, stature and general development have improved to a degree that can almost be measured in inches. This change is so general and has been so rapid that it cannot be attributed to any evolutionary deviation; heredity may play a part in it, but it must in the main

result from environmental circumstances — from better standards of living and, in particular, from better nutrition.

The converse has been seen in war-stricken countries, where mass malnutrition, amounting in places to mass starvation, has seriously stunted the growth of a generation of children. It is in an attempt to evaluate the factors involved that Talbot and his associates have made the studies reported elsewhere in this issue of the *Journal*.

These investigators found that, of a group of over a hundred abnormally short children from two and a half to fifteen years of age, 51 per cent showed no physical disturbance and no hereditary factor to account for the stuntedness. The majority of the patients had presented difficult feeding problems for most of their lives, although the average protein intake, if properly assimilated, was considered to be adequate in all for normal growth. The conclusion was reached that the caloric intake in these cases was more important than the protein itself, because in the absence of sufficient calories from other foods, the protein intake and probably some part of the body protein as well were called on to produce energy.

Attempts to improve the situation by an increased diet were usually unrewarded by any co-operative response on the part of the patients, and further analysis of the group showed that in the majority one or more of certain untoward factors were present. These consisted of mental deficiency or an emotional reaction to poor environmental factors on the part of the patients, of poor family economic situations and of emotional instability, delinquency or psychosis on the part of the mothers.

Correction of the emotional difficulties usually resulted in improved appetite and a gain in weight, but not always in a resumption of growth.

The conclusions may be drawn that growth failure is the indirect result only of malnutrition and that it follows directly from a lack of pituitary growth hormone, this lack being due to the poor nutrition. Such conclusions are strengthened by the fact that improved growth may not result from the acceptance of an adequate diet but does result when methyl testosterone is added to the diet.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

TIGHE — Michael A. Tighe, M.D., of Lowell, died April 8. He was in his sixty-sixth year.

Dr. Tighe received his degree from Harvard Medical School in 1908. He was formerly president of the Middlesex North District Medical Society, and was secretary of the Massachusetts Medical Society. He was a fellow of the American College of Surgeons, New England Obstetrical and Gynecological Society and American Medical Association.

He is survived by his widow, three sons, a daughter, five grandchildren and two sisters.

MISCELLANY

METOPON HYDROCHLORIDE

In 1929, with the funds provided by the Rockefeller Foundation, the National Research Council, through the Committee on Drug Addiction, undertook a co-ordinated program to study drug addiction and search for a nonaddicting analgesic comparable to morphine. The principal participating organizations were the University of Virginia, the University of Michigan, the United States Public Health Service, the Treasury Department's Bureau of Narcotics and the Massachusetts Department of Public Health, which brought together chemical, pharmacologic and clinical facilities for the purpose of the study. Metopon (methyldihydromorphinone hydrochloride) is one of the many compounds made and studied in this co-ordinated effort.

Metopon is a morphine derivative. Pharmacologically, it is qualitatively like morphine even to the properties of tolerance and addiction liability. Chemically, Metopon differs from morphine in three particulars — one double bond of the phenanthrene nucleus has been reduced by hydrogenation, the alcoholic hydroxyl has been replaced by oxygen and a new substituent, a methyl group, has been attached to the phenanthrene nucleus. Studies made thus far indicate that, pharmacologically, Metopon differs from morphine quantitatively in all its important actions — its analgesic effectiveness is at least double and its duration of action is about equal to that of morphine; it is nearly devoid of emetic action; tolerance to it appears to develop more slowly and to disappear more quickly and physical dependence builds up more slowly than with morphine; therapeutic analgesic doses produce little or no respiratory depression and much less mental dullness than do those of morphine; and it is relatively effective by oral administration.

In addition to animal experiments these differences have been established by extensive employment of the drug in two types of patients — those addicted to morphine and others, such as patients in the terminal stages of cancer, needing prolonged pain relief but without previous opiate experience. In morphine addicts, Metopon appears only partially to prevent the impending signs of physical and psychical dependence. In terminal cancer, administered orally, it gives adequate pain relief with little mental dulling, without nausea or vomiting and with slow development of tolerance and dependence. The latter properties place Metopon in a class by itself for the treatment of the chronic suffering of cancer, and it is for that purpose exclusively that it is being manufactured and marketed.

The capsules are put up in bottles of 100, and each capsule contains 3.0 mg. of Metopon hydrochloride. They can be obtained by physicians only from Sharp and Dohme or Parke, Davis and Company, on a regular official narcotic order form, which must be accompanied by a signed statement supplying information concerning the number of patients to be treated and the diagnosis on each. The drug will be distributed *only* for the purpose of oral administration for the relief of chronic pain in cancer cases.

The dose of Metopon hydrochloride is 6.0 to 9.0 mg. (two or three capsules), to be repeated *only* on recurrence of pain, avoiding regular by-the-clock administration. As with morphine, it is most desirable to keep the dose at the lowest level compatible with adequate relief of pain. Therefore, administration should be started with two capsules per dose, increasing to three only if the analgesic effect is insufficient.

Tolerance to any narcotic drug develops more rapidly with excessive dosage and under regular by-the-clock administration. Also, as a rule, the pain of cancer varies widely in intensity from time to time. Pain, therefore, should be the only guide to the time of administration and the dosage level. Tolerance to Metopon hydrochloride develops slowly. It can be delayed or interrupted entirely by withholding the drug occasionally for twelve hours or for as much of that period as the incidence of pain will permit.

To each physician will be sent a record card for each patient to whom Metopon hydrochloride is to be administered. He will be requested to fill out these cards and to return them in the addressed return envelope. He must furnish this record of his patient and his use of Metopon hydrochloride if he wishes to repeat his order of the drug. The principal object of this detailed report is to check the satisfactoriness of the use of Metopon hydrochloride in general practice. The physician's co-operation in making it as complete as possible is earnestly solicited.

The limited use of Metopon hydrochloride as described above has been recommended by the Committee on Drug Addiction, National Research Council, and the committee, with the co-operation of the American Cancer Society, will supervise the distribution of the drug. The committee is composed of Dr. William Charles White, chairman, Washington, D. C., H. J. Anslinger, Commissioner of Narcotics, United States Treasury Department, Washington, D. C., Lyndon F. Small, National Institute of Health, Washington, D. C., and Dr. Nathan B. Eddy, National Institute of Health, Washington, D. C. Queries and comments on Metopon may be directed to Dr. Eddy, who will answer them for the committee.

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CORRESPONDENCE

BASIS OF STUDENT HEALTH SERVICES

To the Editor: In view of the fact that there has been in the past and will be in the future considerable discussion between the relative advantages of a compulsory health-insurance plan and the development of medical-care programs on a voluntary prepaid basis, I think that the editorial "The Third National Conference on Health in Colleges" in the April 19 issue of the *Journal of the American Medical Association* is of interest. This editorial speaks of the organization of student health services on the basis of voluntary prepaid medical-care and hospital insurance. It is common knowledge, however, that at the present time many educational institutions, such as Harvard University, have a well organized medical-care program on a compulsory health-insurance basis.

I am wondering whether the writer of the editorial would like to scrap the program that has been so successful at Harvard, replacing it with a voluntary insurance program.

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BOOK REVIEWS

Pneumoperitoneum Treatment. By Andrew L. Banyai, M.D. 8°, cloth, 376 pp., with 74 illustrations and 16 tables. St. Louis: C. V. Mosby Company, 1946. $6.50.

This book represents a compilation of practically all the literature on the subject of artificial pneumoperitoneum therapy, as well as an evaluation by the author, who has had extensive personal experience as a pioneer in this field. The book does not confine itself to pneumoperitoneum therapy in the narrow sense. It embraces the entire gamut of phthisiotherapy, as well as the many allied chest conditions, and appraises the place of this treatment in the entire scheme of general treatment. The physiology and the physiologic pathology of various chest and abdominal conditions, both tuberculous and nontuberculous, are well considered.

Although artificial pneumoperitoneum therapy is primarily employed in pulmonary tuberculosis, the author also discusses its use in such conditions as pulmonary abscess, bronchial asthma, bronchiectasis and pulmonary emphysema. In addition, he considers its role in abdominal adhesions, ulcerative colitis, intestinal and gastric bleeding and so forth. As yet, however, this form of therapy has not found the universal favor that artificial pneumothorax or thoracoplasty has. The adherents are vehement in their praise, but the greater portion of workers in the field of pulmonary tuberculosis have been lukewarm in their acceptance or have rejected the therapy entirely. This is easily explained by the chronicity, the protean nature and the many forms that such a disease as tuberculosis assumes. Nevertheless, regardless of the merits of artificial pneumoperitoneum therapy, the author has brought the extensive literature of the past ten to fifteen years up to date and has given the profession the benefit of his long and rich experience in this field. Whether this treatment is employed extensively or only occasionally, the book affords a ready reference and intelligent discussion of the many phases pertaining to the subject.

It is for this reason that the book should be read by all men interested in diseases of the chest. It should also find a place on the shelves of all medical libraries as a source of authoritative information.

Mother and Baby Care in Pictures. By Louise Zabriskie, R. N. Third edition, modernized. 8°, cloth, 203 pp., with 229 illustrations and 7 tables. Philadelphia: J. B. Lippincott Company, 1946. $2.00.

This new edition of a manual for mothers has been revised, and many additions and changes have been made in the text. Emphasis is placed on nutrition and the care of the baby. The mechanism of labor and the management of delivery in the hospital and the home are explained in great detail. The immediate care of the baby has been brought up to date, and the material on general care, habits and development during the first year has been entirely reorganized. The text is well organized and excellently illustrated. The plate on the male anatomy is superfluous and not pertinent and could have been omitted without detracting from the value of the book. The ring type of binding is not suitable for hard usage in the home. This manual should prove of value to all mothers and especially to expectant mothers.

Narco-Analysis: A new technique in short-cut psychotherapy: A comparison with other methods: And notes on the barbiturates. By J. Stephen Horsley. 12°, cloth, 134 pp. New York and London: Oxford University Press, 1943. $2.50.

This is the first American edition of this book, which was originally published in England in 1943. It concerns the technic and use of narcoanalysis in psychiatric illness. The author states that the theory of narcoanalysis involves both biochemical and psychodynamic concepts, the former being that persons who for a variety of reasons are sullen, reticent, inhibited or even mute may, during narcosis, converse spontaneously, revealing anxiety conflicts or painful memories from which either consciously or unconsciously they seek refuge, whereas the latter incorporates the generally accepted views of conflict repression and amnesia with reference to their modification by hypnosis and analysis.

One chapter is devoted to a discussion of the barbiturates used in psychiatry, and the writer points out that since the number of barbiturates is increasing, he believes that personal

familiarity with all forms is impossible, and he recommends a number that in his experience have proved successful.

The use of barbiturates is divided into three therapeutic classes: simple hypnotics; those providing a means of producing prolonged narcosis; and those affording a means of establishing contacts with previously reticent or inaccessible patients. In addition, the chapter lists certain conditions that require special caution in their use. Old-age nephritis, liver disease, advanced cardiovascular disease, any tendency to respiratory spasm and toxemias are contraindications to the use of barbiturates.

The rationale of the procedure is explained by the statement that "narcosis is produced very slowly by the gradual administration of a suitable drug, and during the stage of light narcosis, a true hypnotic state is induced by verbal suggestion, and the patient is then amenable to psychological analysis and synthesis." Under the influence of the barbiturates, because of the removal of inhibitions, the latent or repressed conflict comes to the surface, and in a brief period the physician obtains information relevant to the patient's mental state that he could not have obtained in a month by ordinary means.

Following this the psychiatrist determines the salient factors responsible for the condition of the patient, as well as the making of new associations to restore a normal attitude to reality. Two main indications are given for the use of narcoanalysis: to overcome resistance and, in cases due to recent stress, as a quick discovery of the principal emotional upset.

One chapter is devoted to a discussion of the employment of narcoanalysis in wartime. Two interesting reports are included on its use in the British Army and the Royal Navy. The chapters on abreaction and transference are instructive, although the case reports are necessarily brief because of the small size of the book.

The author has presented his material in a clear and concise manner; the bibliography is extensive. The book is recommended as a valuable addition to the psychiatrist's library.

Sex, Marriage and Family. By Thurman B. Rice, M.D. 8°, cloth, 272 pp. Philadelphia: J. B. Lippincott Company, 1946. $2.50.

The author discusses in detail every aspect of marriage, from the basic sexual relation through all the conditions of married life, including psychologic and economic factors and the physical, mental and emotional changes incidental to the change in family status, children and "in-laws." A special chapter is devoted to the problems of marriage in wartime, with emphasis on the status of the returned serviceman. The text is written in a bold, frank manner, with a trace of flippancy, but on the whole, the proffered advice is sound and practical and should prove of value to interested persons of both sexes. It is to be deplored that the word "sex" is used as a synonym for sexual relation rather than in its correct sense.

Autopsy Diagnosis and Technic. By Otto Saphir, M.D. With a foreword by Ludwig Hektoen, M.D. Second edition, revised and enlarged. 12°, cloth, 405 pp., with 69 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. $5.00.

This practical manual of autopsy technic, first published in 1937, has been enlarged by the addition of new material. The discussion of diseases of the breast has been greatly expanded in the interest of the general practitioner and student, since the incidence of breast lesions is high, and there is a vital need of examining this region. New material has been added on accidental death, conditions peculiar to stillborn and newborn infants, nose and accessory sinuses, vitamin deficiencies and certain tropical diseases. Emphasis is placed on anatomically demonstrable lesions. The manual gives merely a diagnostic outline of the gross lesions generally found in structures and organs. Histopathologic lesions are not considered. Only one method of autopsy technic — a modified Rokitansky procedure — is described.

The manual, which is written primarily for the student, laboratory assistant and general practitioner, is well organized and should prove valuable to those interested in gross pathology.

Penicillin: Its practical application. Under the general editorship of Sir Alexander Fleming, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S. 8°, cloth, 380 pp., with 59 illustrations. Philadelphia: Blakiston Company, 1946. $7.00.

The development of penicillin marks a dramatic episode in medical history.

It is appropriate that Sir Alexander Fleming, the discoverer, was invited by the Blakiston Company to edit "a series of independent contributions giving each author's views on the use of penicillin therapy in a disease or in infections of some region of the body," and that the collaborators he selected to take part in this undertaking were his English colleagues whose efforts combined to make the new antibiotic available for clinical use as promptly as possible.

The book is as British as John Bull: it was written by British authors and first printed in Great Britain and emphasizes the work on penicillin in England, although it by no means slights that of American investigators. And, as is so often true in English medical books, the literary style of each chapter is uniformly excellent.

A delightful account is given of penicillin's discovery, its chemistry, manufacture, pharmacology and clinical use. The illustrations are interesting and, indeed, of historical importance, since a picture is reproduced of the original culture plate on which the action of penicillin was observed. At the end of each chapter is a useful list of references leading to more detailed study of the subject under discussion. By way of conclusion, there is an admirable index.

On the whole, this is a noteworthy contribution that is almost faultless. The first printing of the first edition bids fair to rank as a medical classic. Any student or physician can read the monograph with benefit. It offers a restrained account of a most significant medical development; it gives sound advice regarding the proper management of many different clinical conditions; and it is a model of medical literature.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

X-Rays and Radium in the Treatment of Diseases of the Skin. By George M. MacKee, M.D., professor of clinical dermatology and director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University; and Anthony C. Cipollaro, M.D., assistant professor of dermatology and assistant director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University. With a contribution by Hamilton Montgomery, M.D., associate professor of dermatology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Fourth edition, thoroughly revised. 8°, cloth, 668 pp., with 321 illustrations. Philadelphia: Lea and Febiger, 1946. $10.00.

Dr. MacKee and his collaborators have thoroughly revised this fourth edition of a standard work, first published in 1921 and revised from time to time. The authors have attempted to correlate the special knowledge of the dermatologist and the radiologist and to include the essential elements of physics and biology and seem to have succeeded in their objective. The first two chapters are devoted to a short and concise history of roentgen rays and radioactive elements. These are followed by chapters on physics and technic and finally on radiation of the skin in general and on the various diseases of the skin and tumors amenable to radiation therapy. The last chapter is on the medicolegal aspects of roentgen and radium therapy. A selective bibliography is appended to each chapter, and a good index concludes the volume. The book is well printed in every way and is a credit to the publisher. The work is recommended for all medical libraries and to physicians and others interested in the subject.

Progress in Neurology and Psychiatry: An annual review. Edited by E. A. Spiegel, M.D., professor and head of the Department of Experimental Neurology, Temple University School of Medicine. 8°, cloth, 708 pp. New York: Grune and Stratton, 1946. $8.00.

This volume begins a new series of annual reviews in the fields of neurology and psychiatry in all their aspects. It is based primarily on the literature covering the period from December, 1944, to December, 1945. There are thirty-nine articles on pertinent subjects by recognized authorities and to each article is appended a complete list of references for the period covered. As an example, the review on pharmacology of the nervous system has a bibliography of seven hundred and twenty-eight articles. The objective of the work is to provide critical surveys of basic theoretical foundations, as well as the various clinical aspects of neurology and psychiatry. The book is well printed on a good soft paper. A slightly bolder type, however, would make for easier reading. The volume and its continuations are recommended for all medical libraries and should prove useful to all specialists in its fields.

Medical Services by Government: Local, state and federal. By Bernhard J. Stern, Ph.D., lecturer in sociology, Columbia University. A publication comprising studies of the Committee on Medicine and the Changing Order of the New York Academy of Medicine. 8°, cloth, 208 pp. New York: The Commonwealth Fund, 1946. $1.50.

The author in this monograph furnishes an inventory, in historical perspective, of medical services now being provided directly and indirectly by government agencies on all levels — local, state and federal. The term "medical services" is understood to include all diagnostic and therapeutic, general and specialized services given to patients at home, in a doctor's office or at clinics, hospitals, schools or other institutions. It does not include community preventive measures, such as health education, sanitation, sewerage and water supply. The author has tried to indicate the pattern, scope, trends and nature of the medical services now being given and financed by all governmental agencies, and has succeeded in attaining his objective. The material is well arranged, well written and well published. This volume, as well as all others in the series, is recommended for medical, public-health and social libraries.

Allergy. By Erich Urbach, M.D., chief, Allergy Department, Jewish Hospital, Philadelphia, and associate in dermatology, University of Pennsylvania School of Medicine; and Philip M. Gottlieb, M.D., associate, Allergy Department, Jewish Hospital, Philadelphia, and instructor in medicine, University of Pennsylvania School of Medicine. Second edition. 4°, cloth, 968 pp., with 412 illustrations and 64 tables. New York: Grune and Stratton, 1946. $12.00.

The first edition of this treatise was published in 1943, and it has been found necessary to revise this second edition. Nearly 1300 new references have been inserted in the text, and the material has been increased by more than 10 per cent. Twenty-one new illustrations have been included. The following new sections have been added: Rh factor, allergic bronchitis and cough, eosinophilic erythredema and the psychosomatic aspects of allergy. Many sections have been materially enlarged. An appendix comprising a complete list of the concentrations used in patch testing has been added to the text. A double-column format has been used to cut down the bulkiness of the volume. The text is well printed with a good type on heavy coated paper. The weight of the volume could have been reduced by the use of a lighter uncoated paper. This treatise should be in all reference collections in medical libraries.

Allergy in Practice. By Samuel M. Feinberg, M.D., associate professor of medicine and chief, Division of Allergy, Northwestern University Medical School. With the collaboration of Oren C. Durham, chief botanist, Abbott Laboratories, and Carl A. Dragstedt, Ph.D., M.D., professor and chairman, Department of Pharmacology, Northwestern University Medical School. Second edition. 8°, cloth, 838 pp., with 34 figures and 25 tables. Chicago: Year Book Publishers, Incorporated, 1946. $10.50.

This standard textbook has been revised in the light of recent advances in the subject since the publication of the first edition in 1944. The chapter on pollens and pollen allergy has been brought up to date, and pollen counts have been interpreted in the light of the newest survey methods. These new procedures in pollen counting are published for the first time. New material includes discussions on periarteritis nodosa, rheumatic fever, acute disseminated lupus erythematosus and the status of histamine and histamine antagonists in allergy. The text is well printed with a good readable type on good paper. An extensive bibliography is appended to each chapter. The volume is recommended for all medical libraries and should prove valuable to physicians interested in the subject.

NOTICES

NEW ENGLAND HEALTH INSTITUTE

The first meeting of the New England Health Institute since the war will be held at the University of New Hampshire, Durham, on June 16, 17 and 18. Train service from Boston to Durham is available about every two hours.

The program will include symposiums on public-health administration, health problems in welfare and geriatrics, industrial health and hygiene, vital statistics, maternal and child health, public-health nursing, communicable diseases, tuberculosis control and school health and health education.

Since a large attendance is expected, all who plan to participate are urged to register early. Further information regarding the Institute will be furnished on application to the Executive Committee, New Hampshire State Health Department, Concord.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, May 28.

PROGRAM

1:15 p.m. Luncheon. Vanderbilt Hall, Harvard Medical School (price, 70 cents).

3:00 p.m. Clinical Presentation of Dental Patients and Dental Subjects. Paul K. Losch, D.M.D. Main Amphitheater, Children's Hospital.

Members of the medical profession and students are cordially invited to attend.

5:30 p.m. Refreshments. Longwood Towers.

6:30 p.m. Dinner. Longwood Towers (price, including tax, $2.50). For members and friends.

7:30 p.m. Child Health in Britain. Dr. Alan Moncrieff, Nuffield Professor of Child Health, University of London; physician, Hospital for Sick Children, Great Ormond Street, London.

Members of the medical profession and students are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 29

MONDAY, JUNE 2

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, JUNE 3

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, JUNE 4

*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater, Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

MAY 26. New England Heart Association. Page 772, issue of May 15.

MAY 28. New England Pediatric Society. Notice above.

JUNE 1–7. American Board of Obstetrics and Gynecology. Page 772, issue of May 15.

(*Notices continued on page xv*)